BRAIN

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A Journal of Neurology

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CONTENTS.

	PAGE
The Great Vein of Galen and the Syndrome of Increased Intracranial Pressure. T. H. B. Bedford	1
Progressive Paralysis of the Nervus Interosseus Dorsalis. Henry W. Woltman and James R. Learmonth	25
Subdural False Membrane or Hæmatoma (Pachymeningitis Interna Hæmorrhagica) in Carcinomatosis and Sarcomatosis of the Dura Mater. Dorothy S. Russell and Hugh Cairns	32
Hour-Glass or Dumb-Bell Tumours of the Spine. Henry Cohen ...	49
The Cerebrospinal Fluid in Multiple Sclerosis. H. Houston Merritt ...	56
The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements, Forced Grasping, Spasticity, and Vasomotor Disturbance. Margaret A. Kennard, H. R. Viets and J. F. Fulton	69
Familial Periodic Paralysis and its Transition into Spinal Muscular Atrophy. A. Biemond and A. Polak Daniels	91
An Analysis of Disturbed Function in Aphasia. Konrad Zucker ...	109
Senile Plaques. L. Bouman	128
The Intrinsic Nervous Mechanism of the Human Lung. John B. Gaylor	143
Subacute Spino-Cerebellar Degeneration occurring in Elderly Patients. J. G. Greenfield	161
Cholesteatoma of the Middle and Posterior Cranial Fossæ. G. L. Montgomery and D. I. C. Finlayson	177
The Myotonia Acquisita in Relation to the Postneuritic Muscular Hypertrophies. Knud H. Krabbe	184
The Participation of the Neuroglia in the Formation of Myelin in the Prenatal Infantile Brain. Bernard J. Alpers and Webb Haymaker...	195
Observations on Referred Pain. Charles Bolton	211
Tuberous Sclerosis with Epilepsy (Epiloia) in Identical Twins. Howard Fabing...	227
A Study of the Muscle Chemistry in Myasthenia Gravis, Pseudo-hypertrophic Muscular Dystrophy and Myotonia. S. Nevin ...	239

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PAGE

The Venous System of the Velum Interpositum of the Rhesus Monkey and the Effect of Experimental Occlusion of the Great Vein of Galen. T. H. B. Bedford 255

Autonomic Control of the Urinary Bladder. Orthello R. Langworthy, David L. Reeves and Edward S. Tauber... 266

The Generalized and Vertebral Forms of Myeloma: Their Cerebral and Spinal Complications. Peter G. Denker and Samuel Brock ... 291

Effects of Experimental Lesions of the Posterior Columns in *Macacus rhesus* Monkeys. A. Ferraro and S. E. Barrera 307

Inorganic Constituents of Cerebrospinal Fluid *v.* Ventricular and Loculated Fluid. Robert Alexander McCance and Elsie Watchorn 333

The Relationship between the Sugar and Urea Contents of the Blood and Cerebrospinal Fluid. J. N. Cumings and E. Arnold Carmichael ... 338

The Berger Rhythm: Potential Changes from the Occipital Lobes in Man. E. D. Adrian and B. H. C. Matthews 355

Spinal Shock and some Features in Isolation-Alteration of the Spinal Cord in Cats. E. G. T. Liddell 386

Congenital Dermal Sinuses: A Source of Spinal Meningeal Infection and Subdural Abscesses. A. Earl Walker and Paul C. Bucy 401

Some Aspects of Sweat Secretion in Man: with Special Reference to the Action of Pilocarpine. W. C. Wilson 422

Localized Abnormal Flushing and Sweating on Eating. V. Uprus, J. B. Gaylor and E. Arnold Carmichael 443

Spinal Terminations of the Projection Fibres from the Motor Cortex of Primates. E. C. Hoff and H. E. Hoff 454

Acoustic Value of the Several Components of the Auditory Pathway. Fred A. Mettler, Glen Finch, Edward Girden and Elmer Culler ... 475

Some Observations on the Cerebral Veins. J. E. A. O'Connell... ... 484

Hemichorea associated with a Lesion of the Corpus Luysii. James Purdon Martin and N. S. Alcock 504

The Disturbances after Laminar Thermo-Coagulation of the Motor Cerebral Cortex. J. G. Dusser de Barenne 517

Notices of Recent Publications 85, 206, 350, 527

March, 1934.

BRAIN.

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THE GREAT VEIN OF GALEN AND THE SYNDROME OF INCREASED INTRACRANIAL PRESSURE.

BY T. H. B. BEDFORD.

(From the Department of Pharmacology, Manchester University.)

This inquiry constitutes an attempt to examine the data on which is based the theory that interference with the flow of blood through the great vein of Galen may bring about a state of increased intracranial pressure. Since Stopford [24] advanced the view that the increased intracranial pressure which accompanies cerebral tumour is frequently a consequence of an obstruction to the flow of blood through this vein, the subject has become one of the greatest importance. The evidence that obstruction to the great vein of Galen may bring about a state of increased intracranial pressure has been drawn from three different sources: (1) The post-mortem finding of a communicating hydrocephalus in cases of thrombosis of the great vein of Galen or of the straight sinus and in which no other cause can be assigned for the hydrocephalus; (2) the experiments of Dandy and Blackfan [6] on the effect of occlusion of the great vein of Galen in dogs; (3) certain deductions based on a consideration of the anatomy of the great vein of Galen and of the relative incidence of hydrocephalus in cases of cerebral tumours localized in different parts of the brain.

The Formation of the Cerebrospinal Fluid.

Before proceeding to a detailed examination of the evidence derived from these different sources, it is proposed to consider very briefly the manner of formation and absorption of the cerebrospinal fluid. The cerebrospinal fluid is formed mainly by the choroid plexuses of the lateral ventricles and to a less extent by those of the third and fourth

ventricles. Although there is considerable evidence in favour of the view that the fluid is formed by a simple filtration and not by vital secretion (Mestrezat [19]), complete proof is lacking and the subject awaits further investigation. In this connection it is important to note that those who maintain that an increased production of cerebrospinal fluid follows obstruction to the venous outflow from the choroid plexuses are almost compelled to accept the theory of simple filtration, for it is unlikely that an increased secretion, which is a vital process, could be induced by venous obstruction. If, for the time being, we accept the theory of filtration, it becomes apparent that the amount of fluid formed over a given period will be determined by two main factors: (1) The height of the choroidal capillary pressure; (2) the capillary circulation rate. Total obstruction to the entire venous return of the plexuses, although raising the capillary pressure, would soon be followed by concentration of the non-filtrable constituents of the blood, cessation of filtration and infarction of the organs. On the other hand an intermittent or incomplete obstruction might raise the capillary pressure without seriously diminishing the rate of flow through the capillaries, and under these circumstances filtration could proceed unchecked and might be increased.

The Absorption of Cerebrospinal Fluid.

The evidence regarding the method by which the cerebrospinal fluid is absorbed is highly conflicting. Two main schools of thought exist. Weed [25], as a result of experiments based on the original investigations of Key and Retzius [17], believes that the cerebrospinal fluid is absorbed mainly through the Pacchionian granulations or "arachnoid villi" into the cerebral venous sinuses and to a very slight extent into the lymphatic system. Confirmatory evidence has been supplied by Dixon and Halliburton [10], and by Frazier and Peet [12], and this would seem to be the favoured theory. On the other hand Dandy and Blackfan [6], as a result of experiments based largely on the excretion by the kidneys of diffusible dyes after their introduction into the subarachnoid space, conclude that the absorption of cerebrospinal fluid is a "diffuse process from the entire subarachnoid space," and that the fluid finds its way directly into the capillaries there. Still more recently Dandy [8] has provided further experimental evidence in favour of this theory. Although a detailed discussion of the phenomenon of the absorption of the cerebrospinal fluid would be out of place here, it is important to realize that on the basis of either theory an excessive formation

of fluid need not of itself give rise to a state of increased intracranial pressure. This can occur (1) if the fluid is formed at a greater rate than that at which the absorption mechanism can deal with it, or (2) if it is formed in such quantities that the channels which normally drain it away become functionally too small to prevent its accumulation within the ventricles. As regards the first possibility Cushing [5] believes that a blocking of the arachnoid villi by extravasated blood-cells or products of inflammation may be an important cause of idiopathic hydrocephalus. There is, however, no evidence that the absorption mechanism normally is ever unable to deal with the maximum amount of fluid that the plexuses are capable of producing. As regards the second possibility, Dandy [7] has brought forward evidence that an obstruction to a main conducting channel, which need not always be complete, may be followed by hydrocephalus. Stopford [24], however, in order to account for the relatively slight distension of the fourth ventricle as compared with that of the lateral and the third ventricles in certain cases of hydrocephalus associated with cerebral tumours in which there has been no apparent obstruction of the aqueduct, considers that owing to obstruction of the great vein of Galen, "the production of fluid by the choroid plexuses is so great that only a proportion of it can be drained off along the aqueduct; consequently the pressure in these cavities (the lateral and the third ventricles) rapidly rises and dilatation results." To sum up, it would appear on purely theoretical grounds that obstruction to the great vein of Galen may, under certain circumstances, lead to an increased production of cerebrospinal fluid. An excessive production of cerebrospinal fluid need not of itself bring about a state of increased intracranial pressure. Such might occur in the special circumstances in which conduction or absorption is inadequate. We are now in a position to examine the data on which is based the theory that obstruction to the great vein of Galen causes increased intracranial pressure

(1) *Hydrocephalus following Thrombosis of the Great Vein of Galen or of the Straight Sinus.*

Dandy [7] has reviewed the literature relating to the finding at autopsy of hydrocephalus in cases of thrombosis of the great vein of Galen or of the straight sinus. In his paper, which appeared in 1919, he states: "The authentic cases in which thrombosis of the vein of Galen or straight sinus has caused hydrocephalus are few but apparently

definite. Newman (1882) reports a case, and Browning (1887) another." A careful search through the literature subsequently to Dandy's paper has failed to trace any further cases. It would appear, therefore, that since 1887 no case has been recorded in which hydrocephalus may have been brought about by thrombosis of the great vein of Galen or of the straight sinus. As the authenticity of the cases reported by Newman and Browning has so far never been disputed, and in view of the importance attached to them by Dandy and by most subsequent writers, it is proposed to consider each in detail.

The subject of Browning's excellent paper [4] was a girl, aged 6, who died in coma after an illness of three months. The symptoms were vague and indefinite. Autopsy revealed a dilatation of both lateral chambers, of the third and fourth ventricles and of the connecting iter; the straight sinus contained an organizing thrombus which, if not entirely blocking its lumen, very nearly did so. The thrombosis was the end-result of a perisinusitis of long standing. It will be observed that so far the case is beyond criticism. When, however, Browning came to examine the superior longitudinal sinus he found that although its lumen was everywhere free from antemortem clot, the walls of the sinus itself were involved in a perisinusitis similar to that affecting the straight sinus, but which on naked-eye examination did not appear to be of as long standing as that of the latter. The lacunæ laterales were especially affected and seemed for the greater part to have been reduced to fibrous cords. Unfortunately Browning made no histological investigations and thus we lack more precise details of the extent and relative duration of the lesions and also of the condition of the subarachnoid space generally. There is, however, sufficient evidence that the arachnoid villi were seriously damaged, a finding which according to Weed [25] and to Cushing [5] may have accounted for the hydrocephalus. Thus the case is by no means free from complications and cannot therefore be admitted as an example of hydrocephalus following thrombosis of the straight sinus.

Newman's paper [20] unfortunately lacks the wealth of detail which is to be found in Browning's. The patient was a man, aged 55, who died in coma after an illness of about three months' duration. In vagueness of symptoms the case somewhat resembled the previous one. At autopsy the lateral ventricles were found to be considerably dilated and each contained an accumulation of about 4½ oz. of clear straw-coloured fluid which on examination was found to contain 0·09 per cent. of "albuminous matter"; microscopical examination of the sediment

revealed a "few leucocytes and one or two crystals of cholesterine and margarine." The choroid plexuses were unusually vascular and there was a small whitish adherent clot at the point where the great vein of Galen and the inferior longitudinal sinus unite to form the straight sinus. None of the other vessels or sinuses contained clot. Unfortunately Newman failed to record the condition of the remaining ventricles and of the aqueduct. It is impossible, therefore, to be certain that the case was one of communicating hydrocephalus. The presence within the ventricles of a straw-colour fluid of relatively high albumin content and containing a few leucocytes would seem to suggest that the hydrocephalus had followed meningitis (Levinson [18]). However, in the absence of essential details it is impossible to determine its true nature.

It would appear, therefore, that an authentic case in which hydrocephalus has resulted from thrombosis of the great vein of Galen or of the straight sinus has so far not been recorded. On the other hand there appears to be definite evidence that thrombosis of the straight sinus and of the great vein of Galen can occur without the development of hydrocephalus. A case is recorded in St. George's Hospital Reports [21] of an anæmic girl, aged 20, in which a thrombosis of the straight sinus and of the great vein of Galen was discovered at autopsy. The clot is described as being "firm and of red colour mottled with white." The ventricles contained no excess of fluid and there were no additional lesions of note. It must be admitted, however, that it is difficult to form an estimate of the probable duration of the lesion.

(2) *Experimental Occlusion of the Great Vein of Galen.*

In a series of ten dogs, Dandy and Blackfan [6] occluded the great vein of Galen and the straight sinus at different points. The animals were kept alive for three to three and a half months. When they were killed it was discovered that hydrocephalus had developed in one instance only. The hydrocephalus was communicating in type and only moderate in degree; it was found in this particular case that the vein had been obstructed close to its point of origin. In the remaining nine cases the ventricles remained unaltered in size. From this single positive result and without any further attempt at confirmation, Dandy and Blackfan concluded that hydrocephalus occurs when the great vein of Galen is obstructed near its origin, and this view has obtained almost universal acceptance. Brain and Strauss, in "Recent Advances in Neurology" (1929), state, "Dandy has shown experimentally that hydrocephalus follows ligation of the great vein of Galen which drains the choroid

plexus, if the ligature be placed at its origin." Stopford, in a paper which appeared in 1926, expresses the opinion that Dandy has provided "convincing experimental evidence" that compression of the great vein of Galen causes an increased production of cerebrospinal fluid, and he states further that "Dandy has recently proved that occlusion of the great vein of Galen in dogs, provided it occurs at the origin of the vein and the development of a collateral circulation is thus prevented, causes internal hydrocephalus on account of the over-production of cerebrospinal fluid."

In order to verify Dandy and Blackfan's pronouncement that experimental obstruction of the great vein of Galen in dogs may be followed by hydrocephalus, this vein has been obstructed at various points along its course in 47 animals. None of these developed hydrocephalus. Thirteen animals died within three weeks as a direct or indirect consequence of operation, while six others, owing to the onset of distemper or of some other diseased condition, had to be destroyed before they had survived Dandy's prescribed period of three months. We are thus left with 28 cases in which the great vein of Galen was successfully obstructed and the animals maintained in good health until they were killed three or four months later. When the brains of these 28 animals were examined it was found that the vein had been obstructed at its origin in 13 instances and comparatively near its origin in 5 others. These cases are especially important, for, as already stated, Dandy and Blackfan believe that hydrocephalus occurs when an obstruction is placed at the origin of the great vein of Galen. Before proceeding to a more detailed consideration of these cases it is proposed to give an account of the operation which was employed in order to occlude the vein and of the methods used to examine the brains after death.

The Operation.

With the exception of one important detail Dandy and Blackfan's technique has been followed as far as their brief account of their method of operation allows. Most breeds of dogs except the very large and heavy types were probably represented. The bulk of the animals, however, were mongrels. Short-haired terriers or small short-haired mongrels were the dogs of choice. The animals varied in age from six months upwards. Dogs under one year were found to be especially liable to develop distemper and when possible were avoided. The most suitable age seemed to lie between one and three years. The anæsthetic employed was morphia and intravenous chloralose.

The cranium is exposed by an ear to ear incision through the shaved scalp. Dandy and Blackfan seem to have worked through a plain opening in the vault of the skull situated over the posterior part of the corpus callosum. They do not indicate that they took any steps to close this opening. All their animals were probably left therefore with a comparatively large aperture in the cranium through which the cerebrospinal fluid may have drained and thus prevented the development of a state of increased intracranial pressure. In order to remedy this defect and to provide a skull which might be expected to function in the manner of a normal cranium, it was decided, after having performed a number of successful operations through an ordinary trephine hole, to open the cranium by turning down an osteoplastic flap. This was accomplished by making a bevelled half trephine cut through the bone over the superior longitudinal sinus and extending the ends downwards by means of bevelled saw cuts. With a little practice it was found possible to cut through the whole thickness of the bone without injuring the underlying dura. The flap was raised in the ordinary way. Care was taken that a piece of temporal muscle remained attached to its base. This is the only important modification made in Dandy and Blackfan's technique. By employing this method of opening the cranium a more convenient and more extensive exposure of the brain is obtained than is provided by a simple trephine hole; the flap, when correctly cut, returns perfectly into position and on killing the animal three months later careful inspection is required in order to determine on which side the cranium has been opened. The flap during operation is protected with saline gauze; the dura is freely opened in a cruciate manner close up to the superior longitudinal sinus which is retracted and the space between the cerebral hemispheres displayed. A retractor is then passed down between the hemispheres and with the aid of a head lamp and suction apparatus the inferior longitudinal vein lying on the corpus callosum and the great vein of Galen as it emerges from under cover of the splenium, are soon brought to light. In separating the hemispheres, veins are frequently torn across and for a time bleed freely This can always be controlled by the application of hot saline. Bleeding from the superior longitudinal sinus, which occasionally is unavoidably injured in the cutting of the flap and is a more formidable complication, can usually be controlled by the application of a fascial graft. In order to expose the point where the veins of Galen unite to form the great vein of Galen it is necessary to divide the splenium of the corpus callosum. This is best accomplished with the aid of some blunt

instrument such as a small aneurysm needle which has been partly straightened. The great vein of Galen is then exposed to view over its entire course, but before it can be taken up with a hook it has to be dissected out from its bed in the velum interpositum. In effecting this, small branches may be torn and for a time there may be slight bleeding which however soon subsides either of its own accord or with the help of hot saline. The vein is now seized with a small blunt hook and a silver clip placed and closed on the desired part of its course. The clips and clip holder were modelled on those used by Dandy and Blackfan and described in their original paper. The clip in position, the hemispheres are allowed to come together and the flap replaced. No attempt is made to suture the dura which at post-mortem examination is found to be entirely re-formed and often only slightly adherent to the cerebrum. The flap does not require to be fixed with sutures but will retain itself in position. A subcutaneous drain is inserted and the skin wound closed with interrupted silkworm sutures.

Treatment after Operation.

The animals suffered surprisingly little discomfort after operation and by the next day were usually on their feet taking food. Sepsis was not found to be a serious complication and if it occurred at all never extended beyond the skin. Normally the wound was completely healed by the tenth or the fourteenth day. Pneumonia accounted for most deaths within the first three weeks and seemed frequently to occur as a complication of acute distemper. Immediately after operation radiograms were taken to determine if the flap fitted accurately and also to obtain some notion of the position of the clip. This was again repeated on the severed head. As this method of investigation provided no information which could not be obtained with greater accuracy by a direct examination of the cranium and brain after death it was later abandoned. A careful watch was maintained in order to discover if the animals developed symptoms which might be related to the onset of a state of increased intracranial pressure and from time to time the fundi were examined ophthalmoscopically for papillœdema. Apart from the occurrence in a few cases of diseases to which dogs in general are subject, the animals remained normal in every respect and ophthalmoscopic examination never revealed any trace of papillœdema. After a period varying from three to six months the animals were killed by decapitation.

Methods employed for the Examination of the Brain after Death.

The severed head was treated in one of the following ways:—

(1) After a careful examination of the osteoplastic flap and underlying dura, the vault of the skull was removed and the entire head placed for fixation in 5 per cent. formol saline. Care was taken not to distort the brain. In order to achieve this the dura was opened only after some degree of fixation had been effected. After three days the brain was removed from the skull, entirely freed from its coverings and allowed to fix for another fortnight. A transverse vertical section was then made through the whole brain somewhat posterior to a point situated midway between the frontal and occipital poles and the size of the lateral and third ventricles and of the aqueduct observed. The exact position of the clip was determined either by a lateral dissection and piecemeal removal of the posterior portion of one cerebral hemisphere, or by a piecemeal removal from above downwards of the upper portion of the cerebral hemispheres and the corpus callosum until the great vein of Galen and its branches were displayed in their entirety. The clip was found always to be enclosed in a fibrous capsule which also involved the vein for a variable distance in front and behind. The amount of obliteration was ascertained with accuracy by passing a fine blunt probe into and along the vein until the obstruction was reached and then by opening up the vessel with a pair of fine scissors.

(2) Immediately after killing, cannulæ were placed in both carotid arteries and the severed head perfused with normal saline until the vessels were washed clean of blood. After perfusion, the vault of the skull was removed and the termination of the great vein of Galen and the straight sinus displayed by cutting away part of the cerebral hemispheres. A small cannula was then introduced into the straight sinus and the great vein of Galen with its tributaries injected with carmine gelatine. The whole brain was then placed in formol saline for hardening. By this method it was possible to demonstrate very clearly the communications of the basilar vein with the veins of the base of the brain, and also the way in which collateral circulation was developed after occlusion of the anterior part of the great vein of Galen. Owing, however, to the deeply seated and relatively inaccessible position of the structures it was desired to inject and to the softness of unfixed brain substance this method was found to be difficult to apply, and success was not always achieved. Finally it was discarded in favour

of a method by which the whole head, after perfusion with normal saline through the carotid arteries, was injected through the external jugular veins with the gelatine mass. The brain was then fixed in the ordinary way. Besides abolishing the necessity of disturbing and distorting the brain before fixation this method was found to be entirely satisfactory for determining the extent and manner of formation of collateral circulation in relation to the occluded vessel. In later experiments this became the method of choice. It was also found possible to fill the veins by introducing the injection mass through the carotid arteries. At one time it was thought that the injection of fluid under pressure through the carotid arteries may possibly modify the size of the ventricular chambers. Experiments were accordingly conducted on normal heads with this in view when it was discovered that the injection of isotonic saline or of gelatine masses failed to modify to any appreciable extent the size of the ventricles.

(3) The head was perfused with normal saline followed by 5 per cent. formol saline and allowed to stand for a few hours, when the brain was removed and placed for further fixation in formol saline. The employment of this method was found essential when the choroid plexuses were required for histological purposes.

The Anatomy of the Great Vein of Galen in the Dog.

In order to obtain a proper understanding of the effects which might reasonably be expected to follow obstruction at various points in the course of the great vein of Galen, it is necessary to possess a knowledge of the anatomy of the vein and of its main branches. A careful search through the relevant literature has failed to reveal a single account which contains the necessary details. Ellenberger and Baum [11] and Bradley [2], describe only the anatomy of the main trunk. Owing to the kindness of a colleague, the heads of a large number of normal dogs have been available, and these have been utilized for the purpose of a more detailed study of the vein and its tributaries. At an early stage in the investigation it was discovered that both the vein itself and its tributaries are subject to marked variations, and the account which follows may be regarded as a description of the average finding. Fig. 2 is a drawing from a brain which has been injected with a carmine-gelatine mass. The upper part of each cerebral hemisphere and the corpus callosum have been removed and the great vein of Galen with its tributaries exposed. It will be observed that in the dog the great vein of Galen is formed in the anterior part of the velum interpositum by the union of

two relatively short veins of Galen and terminates at the anterior border of the tentorium cerebelli where it becomes the straight sinus. The two veins of Galen are themselves formed at a point close to the foramen of Monro by the union of the vein of the corpus striatum and the vein of the choroid plexus. The relatively short course of the veins of Galen and the long course of the great vein of Galen as compared with their

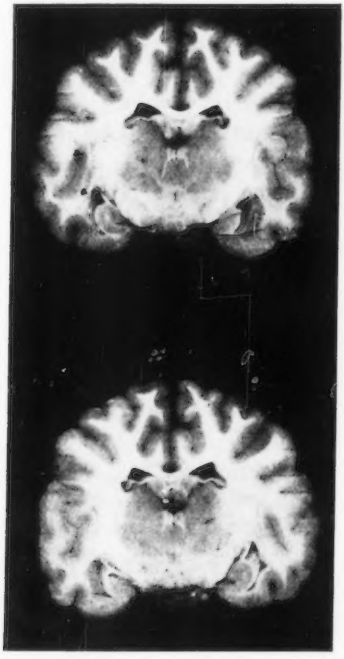

FIG. 1.—Transverse section through the brain of a greyhound in which the posterior part of the great vein of Galen has been occluded for five months. The section has been made anterior to the clip. The ventricles are normal in size.

condition in the human subject are noteworthy. The vein of the corpus striatum is small and very tortuous. It lies in a groove between the optic thalamus and the corpus striatum from which structures it derives most of its blood. The vein of Galen receives tributaries from the choroid plexuses of the lateral ventricles and also communicates with the striate and thalamic branches of the basilar vein. One large tributary which joins the vein of Galen shortly before it unites with its fellow is worthy of special note. In size it exceeds the vein of the corpus striatum;

it drains blood mainly from the optic thalamus but it also receives blood from the choroid plexus of the third ventricle and posteriorly it is in communication with the striate and thalamic branches of the basilar vein and with the veins at the base of the brain. This vessel plays an important part in establishing collateral circulation after occlusion of the great vein of Galen. The vein of Galen is joined at the point where it unites with its fellow of the opposite side to form the great vein of Galen by a number of small but fairly constant vessels from the septum lucidum.

The first tributaries to be received by the great vein of Galen are a number of small venules from the choroid plexus of the third ventricles. Occasionally these venules are united to form a common trunk which seldom attains a size of importance. As often as not, however, they are represented by a leash of venules. Usually a pair of rather stout tributaries is received from the side of the optic thalamus. These vessels, which join the vein of Galen on its under surface, are similarly sometimes represented by a leash of venules. As the great vein of Galen is about to emerge from under cover of the splenium of the corpus callosum it is joined by a pair of veins of moderate size. As these vessels correspond in their position and in the tributaries from which they receive blood to the basilar veins in the terminal part of their course in the human subject, it is proposed to refer to them as the "basilar veins."

It is convenient for the purposes of description to speak of that portion of the great vein of Galen which lies anterior to the point where it is joined by the basilar veins as the anterior part of the great vein of Galen and the portion which lies posterior to this point as the posterior part of the great vein of Galen. Although the point of termination of the basilar veins may vary, this method of describing the great vein of Galen is found to be useful when considering the effect of occluding it at different situations on its course.

Before proceeding to a description of the basilar vein and its communications it is necessary to consider the mode of termination of the veins at the base of the brain. It is noteworthy that in the dog the arrangement of the veins at the base of the brain differs markedly from that found in the human subject. The anterior cerebral vein is a relatively large vessel which drains blood mainly from the under surface of the frontal lobe. It is joined in the region of the anterior perforated spot by a number of veins from the island of Reil and the neighbouring structures. The common trunk so formed does not, however, course round the mid-brain as the basilar vein but passes along the lateral

aspect of the mid-brain, backward and outwards into the tentorium cerebelli and terminates in the lateral sinus. It is proposed to refer to this vessel as the " basal vein." Until the basal vein reaches the lateral aspect of the mid-brain it corresponds in position fairly closely to the basilar vein in the human subject and it is joined by all the tributaries which are normally received in that part of its course by the basilar vein in man. Besides draining blood from the neighbouring structures the vein is joined by a number of important branches direct from the choroid plexus of the descending horn of the lateral ventricle.

The basilar vein in the dog begins in a plexus situated on the upper part of the lateral aspect of the mid-brain where it communicates freely with the tributaries of the basal vein. Its position is similar to that occupied in this part of its course by the basilar vein in man. Before terminating it turns sharply backwards and joins the great vein of Galen on its under surface. Not infrequently it unites with its fellow of the opposite side to form a common trunk. As the basilar vein courses round the crus cerebri it receives branches from the neighbouring cerebral convolutions, the mid-brain and the pulvinar. As already stated, it is in free communication with the thalamic branch of the vein of Galen.

As the great vein of Galen emerges from under cover of the splenium of the corpus callosum and ascends round its posterior border it is joined by a vein which runs from before backwards and rests on the superior surface of the corpus callosum. This is the inferior longitudinal vein. In the dog there is no sinus in the free lower border of the falx cerebri. The inferior longitudinal vein is the last tributary of note to be received by the great vein of Galen before it becomes the straight sinus at the anterior border of the tentorium cerebelli.

Anatomical Changes following Occlusion of the Great Vein of Galen.

From a consideration of the above account of the great vein of Galen and its tributaries it would appear probable that an obstruction applied to any part of its course may be compensated by the development of collateral circulation. It is proposed, therefore, to describe the conditions found on examining the brains of animals in which the great vein of Galen had been occluded at some point on its course for a period of not less than three months' duration.

As already stated, the occluding clip was found always to be enclosed in a fibrous capsule which involved the vein both in front and behind

the clip for a variable distance. In no instance, however, was there extensive obliteration of the vein beyond the clip, and frequently the vessel remained patent on either side directly up to the fibrous capsule.

There are three main sites at which the great vein of Galen may be occluded: the clip may be placed (1) on the anterior part of its course between its point of origin and the point where it is joined by the basilar veins; (2) at the point where it is joined by the basilar vein to obstruct all three vessels, or (3) on the posterior part of its course between the point where it is joined by the basilar veins and its termination in the straight sinus.

(1) In 18 cases a clip was placed successfully on the anterior part of the great vein of Galen, and in 13 of these it was discovered subsequently to be situated close to the origin of the vein. As already stated these cases are especially important, for Dandy and Blackfan claim that hydrocephalus occurs where the great vein of Galen is obstructed at its origin, if a sufficient time is allowed for its development. They are of the opinion that the hydrocephalus of venous obstruction is of slow and gradual onset. In three of the cases the veins of Galen were found to be obliterated at their termination by an extension of the scar tissue from the fibrous capsule surrounding the clip, but in all other instances they remained patent. From a consideration of fig. 2 it will be observed that the only tributaries of any consequence to be received by the great vein of Galen in the anterior part of its course are the veins from the choroid plexus of the third ventricle and the thalamic tributaries. As already stated, these vessels are subject to marked variations. In most instances they were torn and obliterated in the process of dissecting up the great vein of Galen from its bed previous to applying the clip; not uncommonly they were found to be involved by the clip itself or by the resulting scar, and even when not obliterated they did not appear to take any special part in the development of collateral circulation.

In all instances collateral circulation was found to have established itself through the medium of the thalamic tributary of the vein of Galen and the communications of this vessel with the basilar vein. The veins which drain blood from the plexus of the descending horn of the lateral ventricle into the basal vein were found to be dilated so that it would appear that a collateral circulation had also established itself in the substance of the choroid plexus. In no instance were the choroid

plexuses found to present any changes to naked-eye inspection. The cerebral ventricles showed variations in size which corresponded with those of normal controls.

(2) In four instances a clip was successfully placed to include the termination of both basilar veins together with the trunk of the great vein of Galen. On examination after death the occluded vessels were

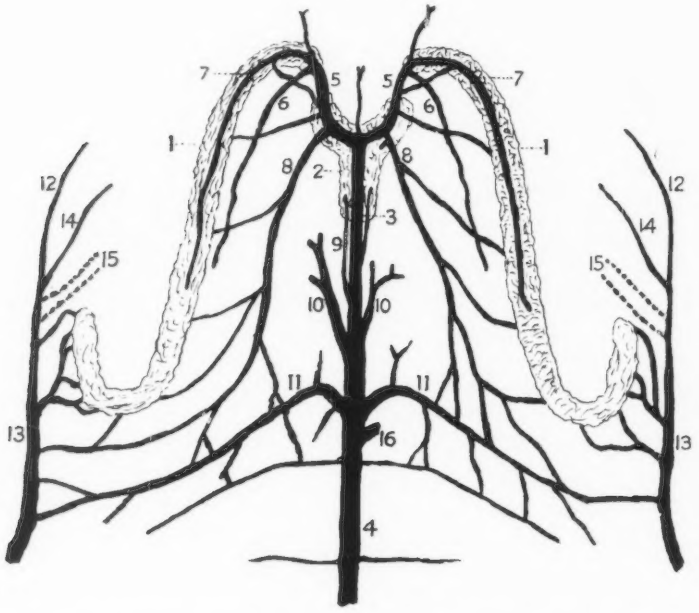

FIG. 2.—Diagrammatic representation of the veins of the velum interpositum and their main communications in the dog. The true relations of the various structures have been distorted and the vessels depicted as occupying one plane. 1. Choroid plexus of lateral ventricle. 2. Choroid plexus of third ventricle. 3. Great vein of Galen. 4. Straight sinus. 5. Vein of Galen. 6. Vein of corpus striatum. 7. Vein of choroid plexus of lateral ventricle. 8. Thalamic tributary of vein of Galen. 9. Tributary of great vein of Galen from choroid plexus of third ventricle. 10. Thalamic tributary of great vein of Galen. 11. Basilar vein. 12. Anterior cerebral vein. 13. Basal vein. 14. Sylvan vein. 15. Deep striate veins. 16. Termination of inferior longitudinal vein.

found to have remained patent close up to the fibrous capsule enclosing the clip. Anteriorly a collateral circulation had developed in the same way as after obstruction to the anterior part of the great vein of Galen. The blood from the basilar vein, now no longer able to enter the great vein of Galen, was found to have passed in a retrograde manner towards the base of the brain and to have escaped through communications

which have already been described into the basal vein. Here again, however, the marked dilatation of the veins which drain blood from the choroid plexus of the descending horn of the lateral ventricle into the basal vein provided definite evidence that a collateral circulation had also developed in the substance of the choroid plexus. The choroid plexuses remained normal to naked-eye inspection and the cerebral ventricles showed only those variations in size which are to be found in normal controls.

(3) The presence of the inferior longitudinal vein would seem to render it possible to occlude the posterior part of the great vein of Galen at two different sites: (*a*) The clip may be placed at the point where it is joined by the inferior longitudinal vein. In two cases the occluding clip was successfully placed on the posterior part of the great vein of Galen so as to include at the same time the termination of the inferior longitudinal vein. The junction of the basilar veins with the great vein of Galen remained patent. Collateral circulation was found to have established itself mainly through the communications of the basilar vein with the basal vein and it was evident that the blood from the obstructed great vein of Galen had escaped into the basilar vein and through these communications into the basal vein. The choroid plexuses presented no change to naked-eye inspection and the ventricles remained normal in size. (*b*) The clip may be placed posterior to the point of union of the inferior longitudinal vein with the great vein of Galen. From consideration of fig. 2, it will be observed that occlusion at this site is equivalent to occluding the straight sinus. In four cases a clip was placed on the posterior part of the great vein of Galen posterior to the point where it is joined by the inferior longitudinal vein. On subsequent examination the inferior longitudinal vein was found in all cases to be uninvolved by clot or scar. Contrary, however, to what might have been expected, the inferior longitudinal vein seemed to take no special part in the formation of collateral circulation which developed in the same way as after the simultaneous occlusion of this vessel and the great vein of Galen. The choroid plexuses remained normal in appearance and the cerebral ventricles presented no deviation in size from the normal.

In addition to the cases above recorded, the great vein of Galen was successfully occluded in nineteen other instances, but, either as a direct result of operation or of the onset of some acute infectious condition such as distemper, the animals died or had to be killed before they had survived a period of three months. In these cases the clip had been

placed on the anterior part of the great vein of Galen in fifteen instances, and the survival period varied from less than a day to eight weeks. Except for the occurrence of toxic changes in the acute infectious cases, the findings were identical with those in animals which survived the full period. Collateral circulation seemed to have developed almost immediately after occlusion of the vein. In two cases the great vein of Galen was successfully occluded at the point where it is joined by the basilar veins, but one animal died after three weeks from lobar pneumonia and the other, owing to the onset of acute distemper, had to be killed after a period of seven weeks. Apart from changes due to the presence of an acute infection, the gross findings in the brain were identical with those in animals which had survived three months. Two animals in which the posterior part of the great vein of Galen had been successfully occluded had to be killed after three weeks owing to acute distemper. Here again, except for changes due to the presence of an acute infection, the findings were identical with those in animals which had survived three months.

From a consideration of the above findings, it would appear that as regards the development of collateral circulation the great vein of Galen can be occluded at only three different sites. The obstruction may be placed: (1) on the anterior part of its course, (2) at the point where it is joined by the basilar veins, (3) on the posterior part of its course.

The Choroid Plexuses after Occlusion of the Great Vein of Galen.

In all cases in which the great vein of Galen had been occluded, a careful examination was made to determine whether the choroid plexuses presented any change to naked-eye inspection. Special attention was paid to that part of the plexuses which occupies the body of the lateral ventricles. It appeared probable from a consideration of the venous return of the plexuses that this part would experience the most intense engorgement. In healthy animals killed in the standard way, the plexuses never presented any change to naked-eye inspection. Realizing, however, that histological changes may possibly take place without bringing about an alteration in gross naked-eye appearance, an attempt was made to examine the plexuses microscopically. This investigation, however, was far from successful. It was found impossible to obtain satisfactory histological preparations unless the brain was injected immediately after death with a formol saline solution. The plexuses from five cases were examined histologically. In three of these the

anterior part, and in two the posterior part, of the great vein of Galen had been occluded. A search was made for the presence of fibrosis, vascular obliteration, altered blood-pigment, and a tendency to simplification of structure owing to degeneration of villi. As far as could be determined from preparations which were often imperfect, the plexuses appeared to remain entirely unchanged. This investigation cannot, however, claim to be exhaustive, and it is conceivable that a more careful examination may reveal structural changes in the plexuses after occlusion of the great vein of Galen. It is realized, however, that even the absence of structural changes does not in any way exclude changes in the functional activities of the plexuses.

Discussion.

From a consideration of the above experiments it would appear that hydrocephalus does not develop after occlusion of the great vein of Galen and that Dandy and Blackfan's finding of hydrocephalus in one case out of a series of ten was not due to obstruction of this vessel but was due to some entirely different cause. Since this work was first undertaken a valuable contribution to the subject has been made by Guleke [14]. This worker successfully occluded the great vein of Galen in nine dogs. In six of these the vein was divided near its origin. The cases survived from a few days to three months. On section eight were found to display no trace of hydrocephalus but one case presented it in a moderate degree. This animal was killed after a survival period of two and a half months. Guleke comments on the free manner in which collateral circulation develops after occlusion of the vein. Unfortunately, however, he does not indicate the precise way in which it is established. In another series of experiments which was primarily devised to investigate the formation of hydrocephalus after blocking of the aqueduct, Guleke occluded the great vein of Galen and the aqueduct either simultaneously or after an interval. Success was achieved in twelve cases and the animals survived from twelve hours to six weeks. Only two developed hydrocephalus; one died within twelve hours of operation and Guleke is of the opinion that the hydrocephalus was due more to operative trauma than to closure of the channels by which the cerebrospinal fluid is removed. In the second case the great vein of Galen had been occluded for two months and the aqueduct blocked for one month before death. As it is proposed in a later paper to consider the effects of experimental obstruction of the aqueduct in dogs, these latter experiments will not now be considered in detail.

It must, however, be admitted that as regards the effects of occlusion of the great vein of Galen, Guleke's findings are in harmony with those of Dandy and Blackfan. Unlike Dandy and Blackfan, however, Guleke does not conclude that simple occlusion of the great vein of Galen causes hydrocephalus; he is of the opinion that some additional circumstance must be present, but does not specify its nature. It remains, therefore, to provide some explanation for the occasional discovery of hydrocephalus in animals which have undergone the operation for occlusion of the great vein of Galen. On perusal of Dandy and Blackfan's and Guleke's papers one is impressed by the total absence of any account of a histological investigation of the hydrocephalic brain and its coverings. Hydrocephalus may occur spontaneously in dogs in association with a number of infective conditions, and it is conceivable that a hydrocephalus indistinguishable from that which Dandy and Blackfan claim to have been caused by obstruction of the great vein of Galen may be the result of an inflammatory lesion at the base of the brain. This lesion may be recent or of considerable standing, and without a careful histological investigation may be recognized only with the greatest difficulty. A search through the literature has failed to trace any account dealing with the precise character of the acquired hydrocephalus in dogs. Nevertheless, one cannot over-emphasize the importance of maintaining a guarded attitude towards the significance of the occasional discovery of hydrocephalus in dogs which have had the great vein of Galen occluded. Before any judgment can be reached it is essential that the brain and its coverings should first be submitted to a careful histological investigation. It is known from clinical observations on the human subject that a relatively high degree of hydrocephalus is compatible with fairly normal activities and behaviour, and it is conceivable that Dandy and Blackfan's and Guleke's animals had either acquired hydrocephalus prior to operation or subsequently to the onset of some form of meningo-encephalitis. Cushing [5] draws attention to the ease with which the arachnoid villi may be blocked by blood and the products of inflammation and expresses the opinion that Dandy and Blackfan have not paid sufficient attention to this aspect of the subject. On the other hand it may be that the total absence of hydrocephalus in the cases now under consideration was due mainly to the practice of killing all animals as soon as they developed an infective condition such as "distemper," a condition to which operated animals seemed to be especially liable. If these animals had not been killed a number would probably have survived the infection, and some of these might have developed a post-

infective hydrocephalus, of which the true nature could have been determined only by a careful histological examination. It is interesting to record that one unoperated animal developed hydrocephalus spontaneously, and although the hydrocephalus was subsequently found to be due in all probability to an obstruction of the aqueduct by organizing inflammatory exudate, the case illustrates the difficulty of determining the nature of a hydrocephalus by mere naked-eye inspection.

FIG. 3.—Transverse sections through the brain of a dog which developed hydrocephalus as a consequence of meningo-encephalitis. The aqueduct was found to be partly blocked by organizing exudate.

An unoperated dog, aged about 12 months, which had been in the laboratory for about three weeks, suddenly had a convulsion and vomited its food. On examination it was found to be somewhat dull and to have a paresis of the hind limbs. No more convulsions were observed, and a few days later, except for the paresis of the hind limbs, the animal appeared to be normal. A week later the paresis began to improve, but although the dog was ultimately able to stand on all four legs the power

of walking never returned completely. After six weeks the animal unexpectedly developed pneumonia and died. At autopsy the brain and meninges appeared to be markedly injected, but they presented no clear evidence of meningitis. No exudate was visible on naked-eye inspection. The cord and its coverings appeared healthy. On sectioning the hardened brain, both lateral chambers were found to be dilated. The aqueduct, however, was not dilated (fig. 3). Histological examination revealed a generalized meningo-encephalitis. The lesion appeared to be subsiding, and the aqueduct was found to have lost its ependymal lining and to be partly blocked by organizing exudate. The spinal cord presented no change. During life repeated ophthalmoscopic examinations failed to reveal the presence of papillœdema.

(3) *The Causation of the Increased Intracranial Pressure associated with the Cerebral Tumours.*

No account of the effects which follow compression of the great vein of Galen would be complete without a reference to Stopford's theory of the origin of the increased intracranial pressure, which is frequently associated with cerebral tumours. While it is not proposed to consider this attractive theory in detail, reference will be made to its most important aspects. In 1926 Stopford [23] expressed the opinion that in man "the great vein of Galen is situated in such a position that it may be compressed against the splenium of the corpus callosum indirectly by tumours occupying sites which are known to give rise most constantly to increased intracranial pressure," and that "such compression is not so likely in the case of tumours occupying situations which are known to cause less frequently increased intracranial pressure." He accepted Dandy and Blackfan's experimental work on the great vein of Galen and suggested "that moderate compression without complete occlusion of the vein is likely to give rise to increased intracranial pressure accompanied by slight or negligible dilatation of the ventricles." In a subsequent paper [24] he concluded, "it seems likely that raised intracranial pressure associated with tumours within the cranium is more commonly due to compression of the great vein of Galen than to any other cause." It would be idle to deny the attractive nature of this explanation of the origin of the increased intracranial pressure of cerebral tumours which certainly accounts for many of the associated phenomena. In order, however, to establish it on a firm basis, it is desirable to prove at the outset (1) that the great vein of Galen is actually obstructed in cases of cerebral tumour associated with hydrocephalus and not in those

in which hydrocephalus is absent, and (2) that compression of the great vein of Galen gives rise to a formation of cerebrospinal fluid which is so excessive that the absorption mechanism is unable to deal with it.

On anatomical grounds and from actual observations, both clinical and pathological, on cases of cerebral tumour Stopford has demonstrated that it is highly probable that the great vein of Galen may be indirectly compressed by subtentorial tumours or by tumours situated in the posterior part of the cerebral hemispheres. Unfortunately, however, the evidence remains largely indirect and no direct demonstration of actual obstruction of the great vein of Galen in the manner Stopford's theory demands has yet been made on the brains of subjects who have died from cerebral tumour. If such evidence were available the theory would be considerably strengthened. It might be thought that the histological appearance of choroid plexuses removed from cases of cerebral tumour would provide evidence that the great vein of Galen is compressed. Saito [22] and Ikedo [16] found the plexuses from the cerebral tumour cases to be œdematous and congested and detected swelling of the endothelial cells. Davis [9] was unable to discover any characteristic lesion, while Zand [26] described changes which were mainly degenerative and corresponded with those found in senile plexuses. Unfortunately these changes may have been induced by a number of causes other than obstruction of the great vein of Galen. Careful controlled work in this direction seems urgently to be needed.

Stopford presents no direct evidence that an increased formation of cerebrospinal fluid follows compression of the great vein of Galen, but seems to rely largely on Dandy and Blackfan's observations on dogs. Although in the experiments described here hydrocephalus did not follow occlusion of the great vein of Galen no matter at what point on its course the obstruction was placed, it would be false to conclude that compression of this vessel in man does not give rise to increased intracranial pressure. Such a view may be criticized on the following grounds: (1) The anatomical arrangement and connections of the veins of the velum interpositum of the dog differ from those found in man; (2) although in the dog total obstruction of the great vein of Galen does not, owing to the plexus-like nature of the veins of the velum interpositum, result in complete stasis, it is possible that if this vessel is actually compressed in man, the obstruction may be both incomplete and intermittent in character. Unfortunately it seems impossible to devise a method by which intermittent compression over long periods could be applied successfully to the great vein of Galen of the dog; (3) while in

the dog it is possible to exclude the presence of hydrocephalus it is difficult entirely to exclude the existence of a state of increased intracranial pressure. It is conceivable, although highly improbable both on clinical and post-mortem evidence that some of the operated animals, although failing to present at autopsy any evidence of dilatation of the ventricles, may have experienced during life increased intracranial pressure.

To sum up, it would seem justifiable to conclude that until conclusive evidence becomes available that an increased formation of cerebrospinal fluid follows compression of the great vein of Galen, any explanation which seeks on such a basis to account for the increased intracranial pressure associated with cerebral tumours cannot be regarded as having advanced beyond the stage of speculation.

Summary.

(1) The authenticity of the two cases of hydrocephalus which Dandy considers to have been caused by obstruction of the great vein of Galen or of the straight sinus is open to question, and evidence is advanced that no indisputable case of hydrocephalus following thrombosis of these venous channels has so far been recorded.

(2) The arrangement and communications of the veins of the velum interpositum of the dog are described and are not identical with those found in man.

(3) After occlusion of the great vein of Galen, no matter at what point on its course, collateral circulation is rapidly established. The choroid plexuses remain unchanged in their gross appearance.

(4) In the dog hydrocephalus does not follow experimental occlusion of the great vein of Galen. It is suggested that the hydrocephalus which was found occasionally by Dandy and Blackfan and by Guleke in dogs in which the great vein of Galen had been occluded was not due to obstruction of this vessel but was of an entirely different ætiology. The hydrocephalus is most easily explained as having its origin in some form of meningo-encephalitis which has led to an obstruction of the normal circulation of cerebrospinal fluid at the base of the brain.

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PROGRESSIVE PARALYSIS OF THE NERVUS INTEROSSEUS DORSALIS.

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FROM time to time we have been confronted with cases of isolated paralysis affecting the nervus interosseus dorsalis, in none of which has a satisfactory explanation of the paralysis been forthcoming. In one case, in which the affected nerve was explored, the only apparent explanation was an anatomical peculiarity of the course of the nerve. A search of the literature has brought little enlightenment, and we are prompted to report our cases in the hope that subsequent investigation may shed light on this singular affection.

REVIEW OF LITERATURE.

Reports of cases of isolated paralysis of the nervus interosseus dorsalis are not common, and in the majority of cases there had been a traumatic origin: for example, after a gunshot wound [6, 8], after a wound by a circular saw [7], and after a sprain intensified by pressure on the nerve during sleep [1].

In the case recorded by Jumentié [4], the paralysis was gradually progressive; the weakness involved the musculus extensor digiti quinti proprius and the adjacent part of the musculus extensor digitorum communis; finally the fourth and fifth fingers could not be extended at their metacarpophalangeal joints, and the affected muscles showed the reaction of degeneration. On the dorsum of the wrist and extending up the fore-arm was a swelling thought to be due to synovitis. We have seen a somewhat similar case in which the nerve was involved in a tumour near the elbow, but we do not propose to include this case in the present paper.

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The details of a case reported by Guillain and Courtellement [2] most nearly resemble those of our own cases.

In July, 1903, a man, aged 40, whose previous history included the possibility of syphilitic infection, found that he was unable easily to extend the fifth finger of his right hand. Ten days later the same disability appeared in the fourth finger. The paralysis spread, and by December, 1903, extension of the third finger became impaired. Subjective and objective sensory disturbances were both absent throughout. At the time of examination the palsy had existed for ten months. Tenderness could be elicited on the posterior surface of the fore-arm, over the point of entrance of the nervus interosseus dorsalis into the fibres of the musculus supinator radii brevis. The paralysis was limited to the extensor muscles of the third, fourth and fifth fingers, and in these muscles partial reaction of degeneration could be demonstrated. The patient was conductor of an orchestra and had held his bâton usually with the fourth and fifth fingers; the writers attributed the paralysis to the repeated movements of pronation and supination necessary in his professional work, and they advised the patient to interrupt this.

A sensory counterpart of the motor affection under review was described by Wartenberg [9] under the designation "cheiralgia paraesthetica"; he regarded the condition as being due to neuritis of the ramus superficialis nervi radialis, and as being analogous to meralgia paraesthetica. The clinical features of his five cases included lively paræsthesiæ or pains along the radial side of the hand, thumb and index finger as well as impairment of sensation in this area, and pain on traction upon or percussion of the affected nerve. In one of his cases, the symptoms appeared seven weeks after a punctured wound which had presumably injured this nerve; in another, pressure of the band of a wrist watch was evidently responsible; in a third, exposure to cold might have been a factor, and in three cases the condition was attributed to over-exertion, but he assumed that a constitutional predisposition might play an important part. In all his cases improvement took place, but residual discomfort persisted in several cases for as long as two and a half years.

Personal Cases.

Case 1.—In September, 1921, a woman aged 43, by occupation a store clerk, presented herself at the Mayo Clinic complaining of weakness of the left hand. Eight years previously, while wrapping bundles of coffee, she had noticed that the left fifth finger "quivered" occasionally. Gradually progressive weakness of the extensor movements of the fingers and wrist had made its appearance. Six and one-half years previously, she had undergone an operation elsewhere for removal of a left cervical rib, but this procedure was not followed by improvement.

On examination it was found that there was complete inability to extend the third, fourth and fifth fingers of the left hand; musculus extensor carpi ulnaris was also functionless. There was some atrophy of the muscles on the dorsal surface of the left fore-arm, which measured 2 cm. less in circumference than its fellow. Roentgenograms disclosed bilateral cervical ribs. Otherwise the examination was entirely negative.

A recent attempt to trace the subsequent history of this patient had been unsuccessful.

Case 2.—In April, 1921, a farmer's wife, aged 37, came to the clinic complaining of weakness of the right hand. At the age of 13 she had been allowed to discontinue instruction on the piano because of difficulty in extending the fifth finger of the right hand. During the three years preceding her examination, this disability had spread to involve other fingers.

The patient was a moderately obese woman. All the muscles of the right fore-arm innervated by the nervus interosseus dorsalis were completely paralysed and markedly atrophied. Exploratory operation with a view to tendon-tranplantation was refused.

Case 3.—In March, 1920, a student, aged 17, sought advice at the clinic because of weakness of the right hand. Four years previously he had survived a severe illness due to rupture of the appendix. Two and a half months after this illness he had discovered that he could not extend the fifth finger of the right hand, and a week later extension of the remaining fingers became impaired; somewhat later still, extension of the thumb became reduced. The paralysis had increased gradually.

On examination it was found that power of active extension of the fingers and thumb was lost. The extensors of the wrist were intact. Reaction of degeneration was present in the paralysed muscles, and the circumference of the right fore-arm was 1 cm. less than that of the left fore-arm. A tender point was discovered over the course of the nerve, 7 cm. below the elbow-joint. Exploration of the nervus interosseus dorsalis was advised, but the patient did not return for this. In 1933 the condition was reported to be unchanged.

Case 4.—In August, 1927, a woman, aged 39, came to the clinic because of a goitre, which had been present since the age of 12. This proved to be a hyperfunctioning adenoma, and thyroidectomy was performed. Four months before her admission she had had pain in the left wrist, left ankle and both knees. One month later she had had a sore throat, accompanied by fever; one month after this she had observed that she could not extend the left thumb.

On examination it was found that there was complete paralysis of the M. abductor pollicis longus and the M. extensores pollicis. Infected tonsils and teeth were removed and light treatment and massage advised. On March 20, 1933, the patient wrote: "The condition is exactly the same. I am still

unable to move my thumb upward, to which I have grown accustomed. I am no longer troubled with the rheumatic pains."

Case 5.—A married woman, aged 34, came to the clinic April 13, 1932, on account of inability to extend the fingers and wrist of the right hand. Three years before she had noticed that she could not extend the fifth finger; six months later the weakness extended to the fourth finger and subsequently the third and second fingers and thumb were affected in that order. One year previously she had noticed wasting on the dorsum of the right fore-arm, and occasionally there had been twinges of sharp shooting pain in that region. The removal of infected teeth two years previously had not retarded the progress of the paralysis. When asleep she habitually kept the right fore-arm under the head.

On examination almost complete paralysis was found of all the muscles supplied by the nervus interosseus dorsalis distal to its branches to musculus extensor carpi radialis brevis. Sensation was intact. Exploration of the nerve was advised and was performed April 19, 1932. A longitudinal incision was made over the interval between musculus extensor carpi ulnaris and musculus extensor digitorum communis. When the supinator brevis was exposed it was found that instead of passing through the supinator the nerve passed superficially between this muscle and the aponeurosis of the common extensor. The nerve had moulded a groove across the fibres of the supinator, and it seemed possible that repeated mechanical trauma imposed on the nerve by the contractions of the supinator brevis might have given rise to neuritis. A direct faradic response to stimulation of the nerve was obtained from the muscles both of the superficial and deep groups, although it was slight in musculus extensor carpi ulnaris and musculus extensor communis digitorum.

In an endeavour to reduce the pressure on the nerve a strip of the extensor aponeurosis, 0·5 cm. in width, was excised over the course of the nerve, and the muscles of the superficial layer were not sutured.

On February 27, 1933, the patient wrote that there had not been any return of power.

Anatomical Considerations.

The normal course of the nervus interosseus dorsalis is through the substance of the supinator brevis muscle. At the lower border of this muscle two branches of distribution appear; one innervates musculus extensor digitorum communis, musculus extensor digiti quinti proprius and musculus extensor carpi ulnaris; the other supplies musculus abductor pollicis longus, musculus extensor pollicis brevis, musculus extensor pollicis longus and musculus extensor indicis proprius (fig. 1). Two anomalous courses are described in anatomical textbooks. In that described by Harburger [3] the branch for the deep group of muscles is divided into two; one twig appears in

the usual situation and proceeds to supply musculus extensor pollicis longus and musculus extensor indicis proprius, the other passes through

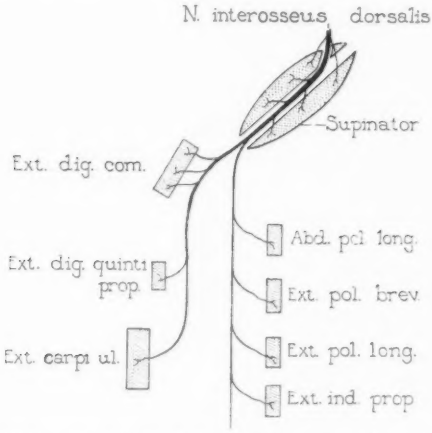

FIG. 1.—Schematic representation of the normal course and distribution of nervus interosseus dorsalis.

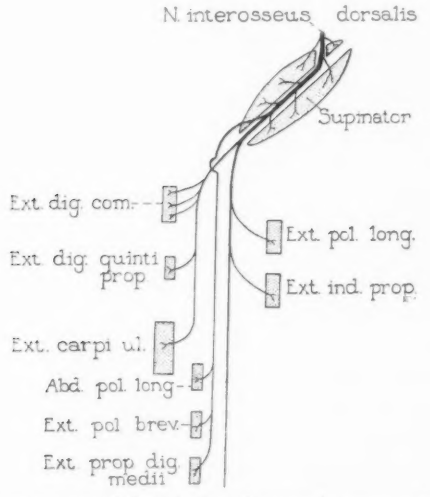

FIG. 2.—Anomalous course and distribution of nervus interosseus dorsalis described by Harburger.

the substance of musculus supinator brevis to appear some distance above its lower border, and is distributed to musculus abductor pollicis longus, musculus extensor pollicis brevis and to a special musculus

extensor proprius digiti medii (fig. 2). The anomaly described by Luschka and by Krause [5] approximates to the arrangement found at operation in our Case 5; the branch of nervus interosseus dorsalis destined for the muscles of the deep group pursues a course superficial to the supinator brevis (fig. 3). This course was taken by the whole nerve in our own case.

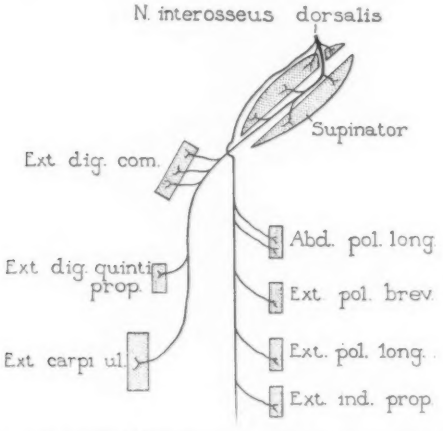

FIG. 3.—Anomalous course and distribution of nervus interosseus dorsalis described by Luschka and by Krause.

COMMENT.

The histories and findings of the patients in our own series of cases have been stripped of all irrelevant details; careful general physical and neurological examinations were made in all, and laboratory data including serological tests and roentgenograms were negative except where reported. In all the cases the paralysis was progressive; as a rule it began with weakness of the extensors of the fifth finger and extended radialward to involve both superficial and deep branches of the nerve. In no instance did the paralysis exceed the distribution of the nervus interosseus dorsalis, and in none were there objective sensory changes although pain was occasionally felt in the fore-arm. Unless some anatomical basis exists, such as seemed likely in the patient whose nerve was explored, we are at a loss to explain the disability. The absence of post-operative improvement in this case is not conclusive evidence against such an anatomical basis, for it is possible that by the time operation was undertaken the interstitial changes in the nerve were already irremediable.

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SUBDURAL FALSE MEMBRANE OR HÆMATOMA (PACHYMENINGITIS INTERNA HÆMORRHAGICA) IN CARCINOMATOSIS AND SARCOMATOSIS OF THE DURA MATER.

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WE report in this paper four cases of subdural false membrane or hæmatoma occurring with metastatic malignant disease of the dura. The association of these pathological conditions with one another is of no great clinical importance, but is of considerable pathological interest since it shows one manner in which subdural hæmatoma can be produced. When we speak of subdural hæmatoma we signify the condition described by different workers under such various terms as "pachymeningitis hæmorrhagica interna," "subdural false membranes," "meningeal apoplexy," "traumatic subdural hæmatoma," and so forth. The pathological lesion is a layer of very vascular granulation tissue which encloses a variable amount of organizing blood-clot and chocolate-coloured fluid and lies between the dura and the arachnoid, usually on the convex surface of one or both cerebral hemispheres. The names employed to describe the condition indicate the diversity of ideas about its nature.

Our attention was first drawn to the combination of subdural hæmatoma and malignant disease of the dura by Case 1 in which an unsuspected subdural hæmatoma was found at operation in a case of malignant disease of the roof of the orbit and overlying dura. Shortly afterwards a second example (Case 2) was encountered in the post-mortem room and subsequent investigation of the records and material of the Bernhard Baron Institute of Pathology at the London Hospital disclosed five further cases.

REPORT OF CASES.

Case 1.—*Secondary carcinoma of the roof of the right orbit and dura. Subdural hæmatoma. Operation: Partial removal of the tumour and hæmatoma.*

History of illness.—J. J., a man aged 64, was first seen on April 21, 1933. Early in 1932 the sight of his right eye became blurred and for ten weeks the

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eyelids were closed. When they opened again there was diplopia and from that time the eyeball became increasingly prominent. There was slight pain in the right eye, later becoming severe. Early in 1933 pain spread to the right zygomatic region and at times to the upper and lower jaw. For a few weeks before admission to hospital his memory was slightly impaired. During the illness he lost 6 kg. in weight and suffered from sciatica in the right leg.

Examination.—Speech and mentality appeared to be normal. There was slight swelling in the right temporal region above the zygoma and the right superficial temporal artery was more prominent than the left. Smell was completely lost at both nostrils. The right optic disc was pale and its edges were blurred; there was no measurable swelling but the retinal veins were engorged. Visual acuity: right, $\frac{2}{36}$; left, $\frac{6}{12}$. Vision in the right eye was limited to the isopters within 25° and mainly above the horizontal meridian. The field and fundus of the left eye were normal.

The right pupil reacted sluggishly to light. There was great displacement of the right eyeball forwards and also slightly downwards, and great diminution of all its movements, especially in an upward direction. The right upper eyelid drooped and there was chemosis of the ocular conjunctiva. Immediately below the inner part of the right supra-orbital ridge a firm, tender nodule, about 2 by 1 cm., could be felt beneath the skin. The right cornea was insensitive. No other neurological signs were found.

There was considerable bronchitis and emphysema, severe osteo-arthritis of the interphalangeal joints of the fingers and of the right hip and both knee-joints. The prostate was enlarged and firm and on the left side slightly nodular. By percussion there was evidently a moderate amount of residual urine. Blood-pressure 145/90 mm. Hg. X-rays showed a large hyperostosis of the roof of the right orbit extending from the supra-orbital ridge to the right anterior clinoid process. This bony thickening appeared to involve also the right frontal and ethmoidal sinuses. The diagnosis made was meningioma of the right side of the olfactory groove invading the frontal and ethmoid sinuses.

Operation, April 29, 1933. The right frontal region was exposed through an osteoplastic flap. Fragments of soft white tumour tissue were found between the pericranium and temporal muscle. The dura over the roof of the orbit and in the adjacent temporal region was thickened by tumour and a thin film of tumour extended upwards over the outer surface of the dura along the course of the meningeal vessels. The inner surface of the dura over the roof of the orbit presented numerous plaques and small nodules of white tumour tissue, but there was no large intradural mass of tumour. The bony roof of the orbit was everywhere thickened, in places up to 1 cm. thick. In the orbit immediately beneath this thick bone was a layer of white tumour.

The dura over the convex surface of the right frontal lobe appeared externally to be normal. When it was opened a glistening dark red

membrane about 0·3 cm. thick was found covering the frontal lobe (fig. 1). It was easily detached from both dura and arachnoid and it extended back beyond the posterior limits of the incision. No fluid was found within this membrane. The roof of the orbit was partially removed, but not so far as to expose the ethmoidal or frontal sinuses, for it was obvious that the tumour was malignant and irremovable. A subtemporal decompression was also made, and fragments of dura and subdural membrane were removed for histological study.

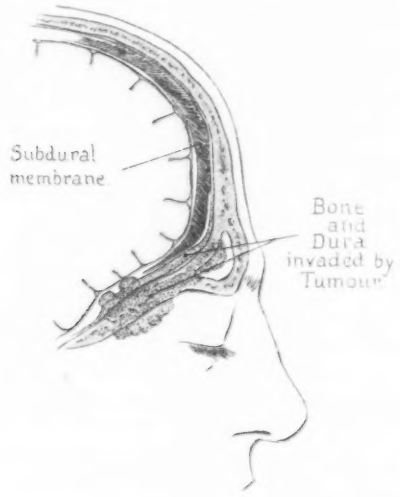

FIG. 1. *Case* 1.—Diagram showing the findings at operation.

Subsequent course.—Recovery from operation was uneventful except for temporary difficulty with micturition. There was complete relief from headache and some recession of proptosis, but no recovery of vision in the right eye. X-ray therapy was applied to the right orbit and right fronto-parietal region. Six months later the condition of the right eyeball was practically unchanged and there were no further cranial symptoms, but the patient was suffering from pain in the right sacral region, so severe as to suggest that the sacrum might be invaded by tumour.

Pathological Examination. (S.D. 865/33).

Macroscopic examination.—The material consisted chiefly of portions of skull and adjacent dura that were visibly infiltrated with growth and had been fixed in 4 per cent. saline formaldehyde. The largest piece of dura was a crescentic slip 5 cm. long and up to 2·5 cm. broad. The

outer surface was rough, gritty, and stained chocolate brown from hæmorrhage. In places a little greyish-white growth was present. Lightly attached to the inner surface were some smooth discrete bosses of pearly-grey growth varying in diameter from 0·3 cm. up to 1·3 by 1·7 cm. The remainder of the inner surface was coated with a translucent buff coloured membrane varying in thickness from less than 0·05 cm. to 0·1 cm. This could easily be stripped from the dura, leaving a smooth orange-coloured surface.

There were also two small rectangles (1·3 by 0·9 cm.) of dura which were macroscopically free from growth. These had been removed from the posterior part of the area exposed at operation and fixed in formaldehyde and Zenker's fluid respectively. The inner surface of each of these was covered with a semi-translucent café-au-lait membrane (0·15 cm. thick) which tended to separate from the dura.

Microscopic examination.—Paraffin blocks were prepared from transverse sections of the dura with buff-coloured membrane and nodules of growth, from portions of the calvaria, after decalcification with nitric acid, and from the rectangles of dura with café au lait membrane and no obvious growth. Sections in this and in subsequent cases were stained with hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, Weigert's fuchselin and neutral red, and, after treatment of formalin-fixed tissue with Zenker's fluid, with phosphotungstic acid-hæmatoxylin.

The tumour is a solid acinar and tubular, polygonal celled carcinoma. There are no special features about the cells that enable the primary site to be identified. In the dura with macroscopic nodules of growth there is extensive carcinomatous infiltration of the outer (periosteal) of the two dense fibrous layers of the dura, associated with a chronic inflammatory infiltration and much recent hæmorrhage. A few trabeculæ of bone are present in the outermost part of this zone. There is little growth in the inner dense layer and it is confined to the lumina of veins and capillaries. Around these vessels is a little infiltration with small lymphocytes and fibroblasts. The areolar layer is thickened and forms the membrane seen with the naked eye. In most places it is occupied by large solid bosses of carcinoma cells; elsewhere it resembles granulation tissue, being composed of very numerous fibroblasts and young capillaries. Many of these capillaries are plugged with growth. In places there are patches of recent hæmorrhage.

In the rectangular pieces of dura without macroscopic growth the membrane that forms the under-surface proves also to be the areolar layer of the dura, greatly thickened. It is as thick as or thicker than

the two dense layers of the dura together (fig. 2). It is composed of a granulation tissue in which numerous spindle fibroblasts containing fibroglia fibrils are interspersed with delicate collagenous fibrils, macrophages containing brown pigment, and small lymphocytes. Within it there is much fibrin, and also recent diffuse hæmorrhage. In places upon its surface are collections of red corpuscles. Many capillaries and veins are enormously dilated and engorged. Some of them are plugged with tumour cells (fig. 3), but others are distended with blood. There are very few tumour cells outside the vessels. The dense layers are unaltered except that capillaries and veins here also are distended with tumour cells; the arteries are free of tumour. Some arteries show reduplication of the elastic lamina. The fragments of calvaria show infiltration of the medullary spaces with masses of tumour cells.

Comment.—This is a case of secondary carcinomatosis of the roof of the orbit and overlying dura associated with subdural hæmatoma. There is a certain amount of clinical evidence that the primary tumour may have been situated in the accessory nasal sinuses or in the prostate. The clinical resemblance of the case to meningioma en plaque of the orbital dura is also of considerable interest. These features, however, are not relevant to our present thesis, which concerns the subdural membrane found at operation. This membrane had given no symptoms before operation, doubtless because of its tenuity. Histologically, however, it is identical with that found in large traumatic or idiopathic subdural hæmatomas. It occupies the areolar layer of the dura which is transformed into a layer of granulation tissue containing numerous greatly dilated and engorged capillaries and veins, areas of recent hæmorrhage, and macrophages containing brown pigment. It is not a reaction to the presence of tumour cells, for these are not present in some parts of the membrane, and when present they are almost entirely confined to the lumina of its vessels. Extension of the tumour in the dura over the frontal lobe has taken place not by direct spread but by permeation of veins and capillaries (fig. 3). The cases that follow suggest that it is the venous obstruction caused by this manner of spread that is of significance in the production of subdural hæmatoma.

Case 2.—Subdural hæmatoma. Secondary carcinomatosis of calvaria and dura mater. General carcinomatosis. Primary diffuse scirrhous carcinoma of stomach. Operation: laparotomy.

E. B., a woman, aged 65, had complained for one year of abdominal pain, vomiting and loss of weight.

On examination a tender mass was felt in the epigastrium, and at operation an inoperable carcinoma of the stomach and numerous intraperitoneal metastases were found. She died ten days after operation, being delirious and finally unconscious in the two days before death.

Summary of Necropsy. (P.M. 269, 1933.)

Moderately contracted stomach with diffuse scirrhous carcinomatous infiltration of its middle part. No ulceration. Secondary carcinomatous deposits in gastro-coronary, cœliac, peripancreatic, lumbar and mesenteric glands. Extensive secondary carcinomatosis of peritoneum of mesentery. Secondary carcinoma of both suprarenal bodies. Secondary carcinomatosis of marrow of right femur, right humerus, ribs and lumbar and lower six thoracic vertebræ. Four small plaques of secondary growth (up to 1 by 0·6 by 0·15 cm.) in submucosa of jejunum. Faint miliary nodules and streaks of growth in very injected periosteum over vault of skull.

Hæmolytic staining of endocardium and intima of all vessels and less conspicuous of other tissues. Parenchymatous degeneration of myocardium. Considerable general atheroma. Post-mortem degeneration and moderate bacterial emphysema of liver. Moderate emphysema and slight myeloid reaction in pulp of spleen. Parenchymatous degeneration of kidneys. Acid digestion of posterior parts of lungs. Atrophy of uterus and of ovaries. Recession of gums from carious teeth. Hirsuties of face. Superficial pressure erosion on each buttock. A slightly wasted, fat woman.

Brain and Meninges.—On removing the top of the skull the outer surface of the dura was roughened, especially over the middle meningeal arteries, by numerous fine linear and pinhead yellowish-white tags, and showed a diffuse brownish discoloration in the frontal region and alongside the superior longitudinal sinus. Grey and pinkish-grey, granular, somewhat dry, lightly adherent ante-mortem thrombus occupied the anterior 6 cm. of this sinus. The sinuses elsewhere contained fluid blood except that a few opaque yellowish-white nodules (up to 0·7 by 0·3 by 0·2 cm.) were attached to the intima of the lateral sinuses, especially the right. During removal of the calvaria the subdural space was accidentally opened and about 60 c.c. of fluid blood with a faint brownish tinge escaped from the right side.

The inner surface of the dura covering the cerebral convexities was everywhere coated with a translucent café-au-lait membrane, varying in thickness from less than 0·05 up to 0·15 cm. This extended on to the falx but was not present in the posterior fossa, nor on either surface of the tentorium cerebelli. There was extensive hæmorrhagic mottling of the membrane, and in many places thin sheets of recent blood-clot appeared to lie within it. Over the right parietal region a mass of

clot (6 by 3 by up to 0·5 cm. thick) was in places attached to the dura and formed a direct continuation of the membrane. Elsewhere it was unattached, and exposed an apparently intact membrane coating the inner surface of the dura. In many places the dura, on section, appeared to be thickened by ill-defined plaques (up to about 3 cm. diameter and from less than 0·05 to 0·1 cm. deep) of firm creamy grey tissue resembling growth.

On the surface of the cerebral convexities were a few shallow depressions. On the right a long comma-shaped depression stretched from 4 cm. behind the frontal pole to the parietal lobe. The expanded hinder end of this depression corresponded with the mass of clot already described. On the left were two small saucer-like depressions over the frontal and parietal lobes respectively. The leptomeninges in these areas had a cloudy, gelatinous appearance, and the sulci were distended with clear faintly straw-coloured fluid. No membrane could be detected on the surface of the arachnoid. On frontal section, after hardening in formaldehyde, the brain appeared normal except for a few cavities in the cerebral white matter caused by post-mortem gas-bacillus infection.

Microscopic examination.—Five strips of dura were selected for paraffin sections from different parts, including the margin of the clot over the right parietal lobe, the margin of a plaque of growth, a transverse section of the left middle meningeal artery, the anterior part of the superior longitudinal sinus and an intimal nodule in the right lateral sinus. In addition a strip of dura was cut on the freezing microtome, and sections were stained with scharlach R and hæmatoxylin. A piece of the bony vault from the frontal region was decalcified in nitric acid and embedded in paraffin. Lastly paraffin sections were prepared from two blocks of the cerebral cortex with its leptomeninges from the right frontal lobe and left Sylvian fissure respectively.

Skull and periosteum.—Many of the medullary spaces, especially in the inner third, contain groups of round and polygonal carcinoma cells. These are associated with many spindle fibroblasts. Islands of coarse-fibred bone are found in several places in the centre of the medullary spaces and on the margins of trabeculæ bounding spaces. The periosteum is greatly infiltrated and thickened by secondary carcinoma and an associated fibroblastic reaction. The capillaries here are greatly engorged. Some have ruptured with extravasation of red corpuscles; others are distended with plugs of tumour cells. There is a little inflammatory infiltration with neutrophil leucocytes and small lymphocytes.

Dura mater.—The changes in the dura vary in different places

according to whether or not the lumina of veins and capillaries are permeated with growth. In a few places, and these are often adjacent to areas with extensive permeation, the whole thickness of the dura is free from growth. The veins and capillaries here are greatly engorged and in places contain a little fibrin. The areolar layer in such areas is slightly thicker than normal from the distension of capillaries and a slight excess of spindle fibroblasts about them. A little diffuse hæmorrhage is sometimes present within it. From such areas there is a sudden transition to others where a considerable or even great thickening of the areolar layer by granulation tissue is associated with a conspicuous permeation of veins and capillaries with tumour cells (fig. 4). Such permeation affects vessels in all layers of the dura but is most conspicuous in the inner dense and areolar layers. The lumina contain a considerable amount of fibrin as well as tumour cells, and organizing thrombus is present in some. Vessels that are not permeated are greatly engorged and hæmorrhages are frequent in their neighbourhood. The extravasated blood sometimes forms a film on the inner surface of the areolar layer and in places such films are undergoing organization. The tissue in the areolar layer is rich in fibrin, spindle fibroblasts and macrophages containing ingested red corpuscles, fatty substances and pigment. A few small lymphocytes are present here and there. In places, especially near the inner surface, a few delicate collagenous fibrils are present.

The dense layers of the dura show, in Herxheimer preparations, a diffuse fatty degeneration, the fatty particles being arranged in longitudinal streaks along the collagen fibres.

The lumen of the superior longitudinal sinus is occupied by antemortem thrombus in which groups of tumour cells are present. A nodule attached to the intima in the right lateral sinus is of similar structure.

The arachnoid membrane over the cerebral cortex has undergone collagenous thickening. The meshes of the underlying pia-arachnoid contain here and there small groups of polygonal cells with round or irregularly lobed nuclei and a vacuolated cytoplasm. They are probably desquamated lining-cells of the pia-arachnoid. In the cortex of the right frontal lobe one perivascular space is infiltrated with cells resembling tumour cells.

Comment.—In this case as in Case 1 a subdural membrane was found in association with extensive carcinomatosis of the dura. On the left side the dura was covered with a membrane of dimensions similar to

that which was found in Case 1. On the right side there was a similar membrane and in addition a mass of clot and a collection of about 60 c.c. of brownish fluid blood which escaped when the dura was opened. With the exception of the terminal delirium and coma there were no symptoms during life that could be attributed to the intracranial condition.

In this case the primary carcinoma of the stomach had given rise to numerous metastases in bones, including the skull. Spread to the dura was by way of the blood-stream: numerous veins and capillaries in all layers of the dura were plugged with tumour cells, and collections of tumour were also found in the superior longitudinal and right lateral sinus. Veins and capillaries not filled with tumour were greatly engorged. It is this engorgement of vessels of the areolar layer of the dura which appears to be the primary factor in the formation of the subdural membrane. The case which follows shows a much earlier stage of the process.

Case 3.—Subdural membrane. Secondary carcinomatosis of dura, skull, long bones, &c. Primary carcinoma of lung.

A. F., a man, aged 44, became ill with pain in the muscles, especially those of the left buttock, seven weeks before his death. He could not sleep, and was depressed, and a few days before his death he became delirious. As a young man he had had syphilis but the Wassermann reaction was negative in the blood taken at necropsy and in the cerebrospinal fluid. The cerebrospinal fluid on the day before his death contained three small lymphocytes per c.mm. and 0·03 per cent. of protein.

Summary of Necropsy. (P.M. 545, 1928.)

Plaques (up to 0·2 cm. thick) of pinkish white firm granular secondary growth scattered over outer surface of dura especially in frontal and temporal regions causing focal, shallow, worm-eaten erosions of inner surface of skull. Layer (less than 0·05 cm. thick) of pink and red organizing clot, showing distinct leashes of capillaries, on inner surface of dura covering both cerebral convexities, especially left (fig. 5). No visible growth in leptomeninges or in substance of brain. Infiltration with firm white secondary growth (up to 0·6 cm. thick) of both temporal muscles near origin. Solid acinar and trabecular large polygonal-celled carcinoma surrounding first branch of bronchus to upper lobe of right lung. Secondary carcinomatosis of bronchial, mediastinal, lumbar, gastro-coronary, right supraclavicular and right axillary lymph-glands; of both suprarenal bodies, marrow of right femur, vertebræ, ribs and sternum. Thin sheet (up to 0·4 cm. thick) of infiltration by secondary growth in origin of vastus internus from right femur.

Great œdema and congestion of right lung and of lower lobe of left lung Slight purulent bronchitis of right lung and of upper lobe of left lung. Collapse of posterior part of right lung and of postero-inferior fringe of upper lobe of left lung. Slightly turbid yellow effusion (60 c.c. each side) in both pleural sacs. Severe parenchymatous degeneration of myocardium. Slight general atheroma. Fatty degeneration and slight periportal fatty infiltration of liver. Severe albuminous and slight fatty degeneration of kidneys. Myeloid reaction in pulp of enlarged spleen (17 by 12 by 5 cm.) with indistinct Malpighian bodies and trabeculæ. Mucous catarrh of stomach with numerous submucous hæmorrhages in wall of body. Healed gastro-jejunostomy stoma (2·7 cm. diam.). Linear scar (2·5 cm.) in posterior wall and lower border of first part of duodenum. Operation scar in upper right quadrant of abdominal wall. Severe gingivitis. Tartar on remaining teeth. Middle ears moist. A somewhat wasted, well-developed man.

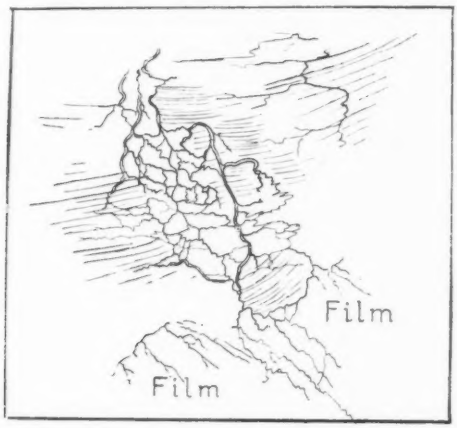

FIG. 5. *Case* 3.—Sketch of inner surface of dura to show engorged capillaries.

Macroscopic.—A portion of the dura from the left cerebral convexity, preserved as a museum specimen, shows conspicuous flat plaques of opaque yellowish growth on the outer surface. The inner surface is mottled: a large part is covered with conspicuous leashes of capillaries which often form an anastomosing net (fig. 5); between and over these are diffuse patches of café-au-lait gelatinous thickening. These patches do not correspond to the external plaques of growth. There are a few small nodules (up to 0·5 cm. diameter) of grey tumour-tissue projecting from the inner surface of the dura in the frontal region, the largest alongside the superior longitudinal sinus. There are many

small areas in which the inner surface of the dura presents a normal glistening appearance.

Microscopic.—Dura : Two pieces were selected for paraffin sections : (1) From the left parietal region with macroscopic growth on the outer surface; (2) from an unspecified site in which macroscopic growth was absent.

(1) The periosteal surface of the dura is greatly thickened by closely aggregated groups and trabeculæ of polygonal tumour cells embedded in a dense collagenous matrix. This forms a layer external to the periosteal dense layer of the dura. The tumour cells frequently occupy the lumina of capillaries and veins. The infiltration does not extend diffusely into the two dense layers of the dura, but in these a large number of blood-vessels are dilated and permeated with tumour cells. The areolar layer is here little changed. It appears œdematous and the inner margin is thickened by a multiplication of spindle fibrocytes. A few red corpuscles are scattered here and there within it, but there is no gross hæmorrhage. A few of its capillaries contain plugs of tumour cells.

(2) The dura as a whole is of normal thickness. There is no diffuse infiltration of any of the layers with growth, but many veins and capillaries in the dense layers are conspicuously permeated by tumour cells mixed with fibrin thrombi. The areolar layer is thicker than normal, on account of the great distension and engorgement of its capillaries (fig. 6). In a few of these are rounded fragments of fibrin, but no tumour cells are present. The tissue about the capillaries appears œdematous and contains an excess of spindle fibroblasts. There is a little diffuse hæmorrhage, and along the inner margin is a thin zone in which spindle fibroblasts are mixed with pigment-containing macrophages.

Skull : A section of the calvaria shows groups of tumour cells in the medullary spaces.

Comment.—This case shows the earliest stage of the process of formation of subdural hæmatoma (fig. 6). Neoplastic permeation of the vessels in the two dense layers of the dura is associated with conspicuous dilatation and engorgement of the capillaries of the areolar layer. Within the areolar layer there is œdema, extravasation of red corpuscles and formation of granulation tissue.

Case 4.—*Subdural membrane. Secondary sarcomatosis of dura, &c. Primary myelosarcoma (Ewing's tumour) of right iliac bone.*

A man, aged 41, had complained for eighteen weeks of pain in the right leg. Examination at first revealed only wasting of the right leg and a

moderate degree of secondary anæmia, but later a mass was felt projecting into the right side of the rectum, and X-rays showed haziness of the inner side of the right sacro-iliac joint. The patient became very weak and wasted. Nine days before death he developed weakness of the right external rectus, lateral and upward nystagmus and slight left facial weakness. The Wassermann reaction of the blood was negative.

Summary of Necropsy. (P.M. 414, 1931.)

Thin layer (up to 0·1 cm. thick) of secondary growth on inner surface and, slightly less, on outer surface of dura over all aspects of frontal, parietal and occipital regions and on basi-occipital and basi-sphenoid, with a little red and brown hæmorrhage in the inner surface of the dura. Area of focal fibrino-purulent leptomeningitis over left posterior parietal cortex. No secondary growth in brain. Primary myelosarcoma of wing of right ilium invading extensively the surrounding soft tissues, dislocating bladder and rectum to left without invasion. Secondly sarcomatous deposits in right lung, head of pancreas, and numerous deposits in marrow of femur and lumbar vertebræ. A few plaques of secondary growth on pleural aspect of left upper ribs.

Atrophy of heart. Moderate general atheroma. Subcapsular cyst, 1 cm. in diameter and containing clear fluid, in liver. Subacute inflammation and myeloid reaction in enlarged spleen (14·5 by 8·5 by 3·5 cm.). Slight dilatation of ureter, pelvis and calyces of right kidney. Œdema and parenchymatous degeneration of right kidney. Congestion and parenchymatous degeneration of left kidney. Numerous fibrous adhesions over upper and middle lobes of right lung and over upper lobe and posterior border of lower lobe of left lung. Severe purulent bronchitis, great œdema and considerable collapse in lower lobe of left lung. Central softening of right suprarenal body. Mucous catarrh of stomach. Colloidal hypertrophy of thyroid gland. Thymus replaced by œdematous connective tissue. Œdema of brain. Middle ears clean. Extremely wasted, edentulous man.

Microscopic examination.—Two strips of dura were selected for paraffin sections. In both there is extensive infiltration of the dense and areolar layers with rounded masses of tumour cells, most of which occupy distended capillaries and veins. In places the tumour appears to spread by perivascular paths and there are more tumour cells outside the vessels than were seen in the preceding cases. Capillaries that are free from tumour are greatly engorged. The areolar layer is greatly thickened by granulation tissue and areas of diffuse hæmorrhage are present near engorged capillaries.

Comment.—In this case the spread of tumour on the inner surface of the dura was more extensive than in the previous cases and the subdural

hæmatoma was very inconspicuous, but histological sections show that the process is essentially the same as in previous cases.

There are in the records three other cases that probably belong to the same category as those just described, but suitable histological preparations are lacking and consequently they do not further our inquiry. In one (P.M. 234, 1914), in a female, aged 52, secondary sarcomatous deposits were present in the skull and one large nodule in the bone and dura on the right side lay immediately outside a "mass of black ante-mortem clot in the subdural space" over the right frontal and parietal lobes; beneath the clot the leptomeninges were stained brown and the brain was compressed. It is probable that this case was analogous to our Case 2. In two further cases slight pachymeningitis interna hæmorrhagica is described.

Discussion.

The association of subdural hæmatoma and malignant disease of the dura does not appear to have been widely recognized. It was reported by Westenhoeffer (1904) in a case of carcinoma of the stomach complicated by fibrino-purulent leptomeningitis due to coliform bacilli. He observed that the capillaries in the false membrane were wide and were often plugged with cancer cells, and concluded that the formation of the membrane was more recent than the dissemination of growth. The term "pachymeningitis hæmorrhagica carcinomatosa" occurs also in the post-mortem summary of Case 49 in Pürckhauer's paper (1929) on carcinoma of the prostate. Wohlwill (1913) alludes, without further comment or description, to two examples of this combination in a series of thirty-two cases of pachymeningitis interna hæmorrhagica; the primary tumours were situated in the breast and penis respectively. The association of the two conditions is not of clinical importance, though doubtless knowledge of its occurrence will enable the observer to explain the manner of death in some cases of malignant disease of the skull and dura. What is of importance is that this association affords an opportunity for studying the histogenesis of subdural hæmatoma, which may be seen here in its earliest stages, death being due to other causes. In our four cases the subdural hæmatoma varied from a thin patchy membrane on the inner surface of the dura to a thick, more extensive membrane that merged with a mass of blood-clot (Case 2). In this case there was also a collection of 60 c.c. of old blood. Owing to an unfortunate error in technique it was impossible to tell whether

this fluid blood lay within the membrane or free within the subdural space.[1]

Study of the microscopic appearances in this series of cases has shown that the membrane forms within the areolar layer of the dura in spite of observations at operation in Case 1. In this case when the dura was reflected there was left behind a glistening red membrane covering the arachnoid and hemisphere, similar to that seen at operations upon large traumatic and idiopathic subdural hæmatomas. But histological examination showed that the membrane, though tending to be detached so easily from the overlying dense dura, was actually nothing more than a greatly thickened areolar layer of the dura.

The formation of the membrane is intimately associated with neoplastic permeation of the capillaries and veins of the dura.

From observations in Case 3 it appears that the earliest change in the production of the membrane is great dilatation and engorgement of the capillaries in the areolar layer while the veins in the dense layers of the dura contain masses of tumour cells (fig. 6). Such an engorgement is associated with œdema and is followed by rupture of capillaries and diffuse extravasation of blood both into the areolar layer and also in greater or less amount into the subdural space. A reactive process then sets in within the areolar layer and a very vascular granulation tissue is formed. There is proliferation of fibroblasts and sprouting of capillaries, while macrophages appear and later become laden with pigment. A few neutrophil leucocytes and lymphocytes are also present in places. With repeated hæmorrhages the areolar layer becomes progressively thicker. In these later stages there is also a conspicuous plugging of capillaries in the areolar layer with growth; tumour cells may be present in groups outside the vessel walls, but it is particularly emphasized that permeation of vessels in the dense layers of the dura is the constant and important histological feature. In many of these vessels fibrinous thrombosis and organization occur.

There is no evidence that the process is excited by the presence of tumour cells in the areolar layer. The membrane is sometimes found in areas where the tumour cells are restricted to the dense dura. Further, it is not an invariable accompaniment of metastatic neoplastic disease of the dura. In this Institute there are records of twenty-four other cases

[1] In a recent case (P.M. 91, 1934) a similar condition was found at necropsy. Thin plaques of growth were present between the vault and the dura and about 100 c.c. of fluid blood and gelatinous clot lay free within the subdural space. The primary growth was in the stomach.

of metastatic neoplastic disease of the dura in which no hæmorrhage or membrane was observed with the naked eye. In six of these a portion of dural metastasis was examined microscopically by us, and in all specimens where sufficient dura was included in the section to form an opinion there was no evidence of any change in the areolar layer. In general there was a massive infiltration of all layers of the dura, or a nodule of growth was present on the inner surface. In a few examples one or two vessels in the immediate neighbourhood showed permeation by growth, but the dural tumour was otherwise entirely extravascular. In this connection it must be recalled that the dura is sometimes involved by direct spread of a glioma from the adjacent brain. In this process the areolar layer is first affected; nevertheless, we have not yet observed an associated subdural hæmatoma or membrane in such cases.

From our studies we conclude that when the dura is involved locally by a circumscribed metastasis or diffusely by direct spread, it is unlikely that a subdural hæmatoma or membrane will also be found. The essential type of neoplastic involvement appears to be a permeation of veins and capillaries of the dense layers of the dura, the tumour having spread to these vessels from the overlying skull. The formation of a subdural membrane or hæmatoma in the areolar layer is the consequence of circulatory disturbance produced in the dura by this permeation.

This notion that subdural membrane and hæmatoma in these cases is produced by mechanical disturbance of the circulation of the dura receives support from the anatomical studies of Ford Robertson (1900) and Charpy (1921). These workers have shown that in the areolar layer immediately adjacent to the endothelium lining the subdural space there is a rich network of large capillaries with ampullary dilatations. These drain outwards into a second plexus in the dense dura, and thence either to the periosteum of the calvaria or to veins that accompany the main meningeal arteries. It is therefore clear that obstruction of the veins in the outer dense layers of the dura will produce dilatation of the capillaries in the inner areolar layer. These capillaries are poorly supported on the side that abuts upon the subdural space, especially when the intracranial pressure is low. It is very probable that the formation of subdural hæmatoma depends to a considerable extent on these peculiar anatomical features of the areolar layer. We have found that in the normal subject the capillaries of the areolar layer are usually empty and collapsed. They are not visible to the naked eye and are seen in histological preparations as clumps of endothelial cells. What

is described by Putnam (1925) as "a growth of capillaries" into the inner layer of the dura in chronic subdural hæmatoma may well be, at least at its beginning, a dilatation of pre-existing normal channels.

We conclude that, in the cases described, the subdural false membrane was the result of mechanical interference with the circulation by permeation of veins and capillaries with growth. The fibroblastic reaction in the areolar layer appeared to be caused by congestion of capillaries, œdema and hæmorrhage. Cases 2 and 3 suggest that the reaction may be initiated by congestion and œdema, but a survey of the material as a whole indicates that hæmorrhage plays the most important part.

A comparison of our cases with examples of pachymeningitis interna hæmorrhagica, some with a history of trauma, others complicating infections such as subacute streptococcal endocarditis, streptococcal septicæmia, pneumonia and syphilis, shows that the histological changes in the areolar layer are similar in all. In none of those that complicate infections is there a histological reaction characteristic of the associated infection. This suggests that vascular changes leading to hæmorrhage are the essential cause of this condition, whatever may be the associated pathological state.

Summary.

(1) Four cases of metastatic neoplastic infiltration of the dura associated with subdural false membrane or hæmatoma are described.

(2) In these cases the subdural false membrane or hæmatoma was formed in the areolar layer of the dura. It was a consequence of dilatation, engorgement and rupture of the capillaries of the areolar layer.

(3) These changes were the result of permeation by growth of the veins and capillaries of the outer dense layers of the dura.

(4) The subdural membrane or hæmatoma was histologically identical with idiopathic "pachymeningitis hæmorrhagica interna" and traumatic subdural hæmatoma.

(5) Subdural false membrane or hæmatoma can be produced entirely by obstruction of the circulation of the dura.

Acknowledgments.

We desire to thank Professor H. M. Turnbull for his help in the preparation of this paper, and Dr. T. G. Reah for assistance in identifying cases in the post-mortem records of former years. The cost of

microphotographs was defrayed by the Charles Bingham Bolton Fund for Neurology.

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PLATE I.

FIG. 2. *Case 1.*—Dura and membrane from posterior part of decompression area. (C) inner and outer dense layers of dura; (A) greatly thickened areolar layer. Rounded dark areas in both layers are vessels filled with growth. Hæmatoxylin and eosin. × 28.

FIG. 3.—Magnified portion of FIG. 2 to show permeation by growth of vessels in inner dense (C) and areolar (A) layers of dura. × 95.

FIG. 4. *Case 2.*—Section of dura showing thickening of areolar layer (A) and permeation by growth of vessels in inner part of dense layers (C) and in areolar layer. Hæmatoxylin and eosin. × 52.

FIG. 6. *Case 3.*—Section of dura showing permeation by growth of vessels in dense layers (C) and great distension of capillaries in areolar layer (A). Hæmatoxylin and eosin. × 78.

PLATE I.

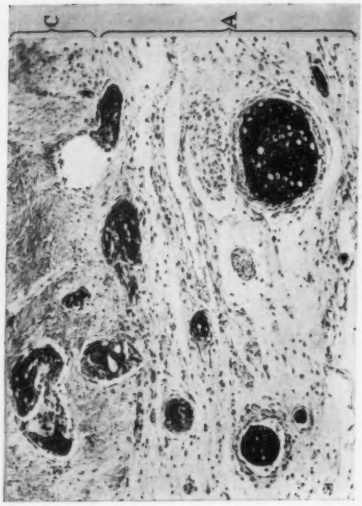

FIG. 3.

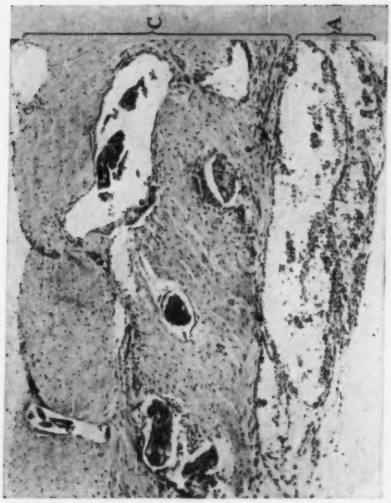

FIG. 6.

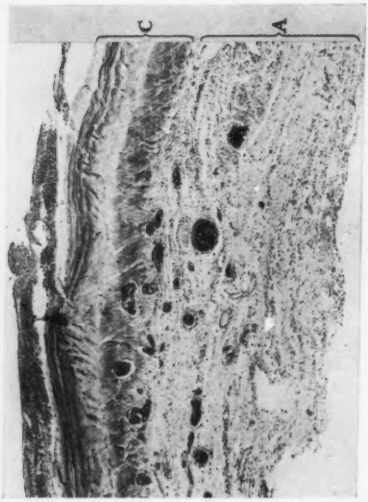

FIG. 2.

FIG. 4.

To illustrate paper by Dorothy S. Russell and Hugh Cairns.

HOUR-GLASS OR DUMB-BELL TUMOURS OF THE SPINE.

BY HENRY COHEN.

Royal Infirmary, Liverpool.

In a series of forty-two cases of compression paraplegia due to tumours of the spine or spinal cord, three cases of so-called hour-glass or dumb-bell tumours have been encountered. No direct reference to these curiously shaped tumours occurs in the literature of this country, and as they are not so uncommon as the absence of a collected series would indicate, I venture to report them. They merit separate clinical description because despite their varied pathology, they display characteristic features which give rise to special problems, both in diagnosis and treatment.

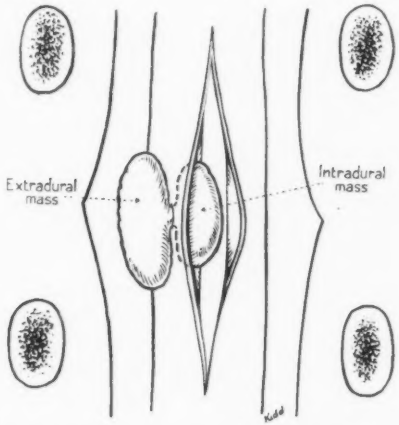

FIG. 1.—Showing diagrammatically an hour-glass tumour wholly intraspinal with connecting stalk passing through dura mater.

Two types of hour-glass tumour in this region have been described:—

(1) Wholly intraspinal, but both extra- and intradural masses are connected by a narrow pedicle (fig. 1). These offer no special problem in diagnosis, but if only extradural exposure is made at operation and the pedicle not observed, the intradural mass, the main factor in compression, may be overlooked.

(2) Those having extra- and intra-dural masses joined by a narrow pedicle passing through an enlarged intervertebral foramen (fig. 2); very rarely the site of the pedicle is interlaminal; in rare instances the intraspinal portion may be again constricted as it penetrates the dura.

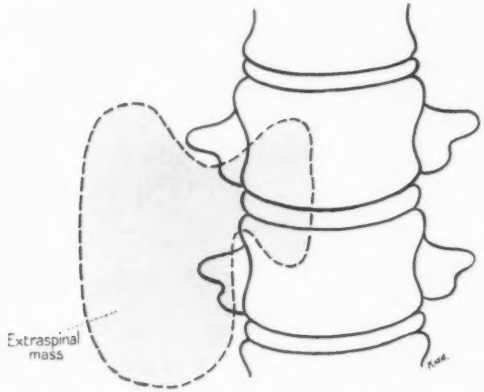

FIG. 2.—Showing diagrammatically an hour-glass tumour with extra- and intra-spinal portions connected by stalk passing through the intervertebral foramen.

SUMMARY OF CASE RECORDS.

Case 1.—Mrs. H., aged 27, complained of aching in left lumbar region on exertion, associated with weakness of left lower limb. Pain first appeared four years ago after her confinement; it gradually increased in severity during the next six months, when after X-ray examination tuberculous disease of the spine was diagnosed. She was kept on a frame for six months but no improvement resulted and in December 1930, after consultation with Sir Robert Jones, a spinal support was worn, with considerable improvement.

On December 23, 1931, clinical examination revealed motor and sensory changes in the distribution of the left second, third and fourth lumbar nerves; no tumour could be palpated in the left lumbar area. The radiogram taken on this day showed the characteristic changes of an hour-glass tumour of the spine (figs. 3 and 4). Three weeks later loss of power in both lower limbs with urinary incontinence and difficult defæcation developed.

Operation (February 6, 1932) by Mr. T. P. McMurray. A tumour encountered in the paravertebral muscles; laminectomy was performed. As the tumour intimately mingled with the cauda equina complete removal was impossible, but pressure was relieved. Pathological report showed the growth to be a fibroblastoma.

She was advised to continue wearing the spinal support, and after the operation she improved considerably. Her doctor reports April 28, 1933,

FIG. 3 (*Case* 1).—Antero-posterior radiogram of the spine showing outline of extraspinal mass (small arrows) and erosion of the bone (large arrow).

To illustrate paper by Henry Cohen.

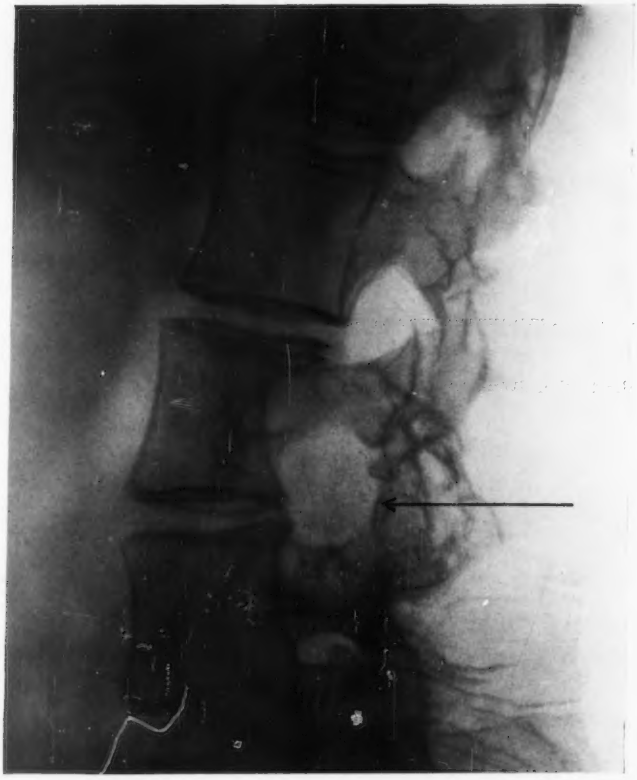

FIG. 4 (*Case* 1).—Lateral radiogram showing characteristic enlargement of left intervertebral foramen between 3rd and 4th lumbar vertebræ, caused by pedicle connecting the two masses.

To illustrate paper by Henry Cohen.

"She has not required any treatment whatsoever since the operation, having enjoyed good health; her back is still in splints and generally she is very comfortable: if she over-exerts herself she gets what she describes as a tired feeling in her back; on one or two occasions she has complained of severe pain in the back and these periods have coincided with the menses. If she leaves off the support, however, her pain returns. She expresses herself as being in very good health."

Case 2.—R. S. H., male, aged 37, was first seen June 14, 1932. He first complained of severe pains radiating down the inner side of the right arm which gradually increased in severity and extent; in 1927, drooping of the right upper eyelid was observed; in 1932, a movable hard lump appeared in the right lower cervical area, and operation was undertaken on the suspicion that the swelling was glandular in origin. A chocolate-coloured grumous material was evacuated and the condition described as a "cystic hæmatoma." Symptoms persisted, and in June 1932, the cervical spine was X-rayed and reported on as follows (fig. 5): "The right halves of the bodies of the sixth and seventh cervical vertebræ showed destructive changes. Extending out from this area into the right supraclavicular (and to a slight extent retroclavicular) region is a homogeneous shadow with well-defined rounded borders. The trachea is displaced slightly towards the left side and very slightly forwards. The X-ray appearances are those of tuberculous disease involving the right half of the body of the seventh cervical vertebra and to a less extent of the sixth cervical vertebra, with the formation of a cold abscess in the right side of the neck."

Clinical examination revealed a fixed, firm, non-fluctuating mass in the right supraclavicular area; wasting of the intrinsic muscles of the right hand and sensory change indicating involvement of the first dorsal nerve, and evidence of a Brown-Séquard syndrome due to pressure on the right side of the spinal cord. Flexion of the head produced constant pain in the left mammary area.

Operation (June 30, 1932) by Professor R. E. Kelly. The mass was exposed from the back after removing the posterior portions of the first and second ribs; it invaded the lower cord of the brachial plexus and contained chocolate-coloured pultaceous material though most of the tumour was firm. The patient died six hours later.

The autopsy was limited to site of operation. No visible secondaries were found. The tumour, which was black, soft and friable, lay on the right side of the vertebral column extending up to the sixth cervical and down to the upper border of the fourth thoracic vertebra. The main mass of the tumour lay on the ventral surface of the first and second ribs, but it entered the spinal canal between the seventh cervical and first thoracic vertebræ, and also between the first and second thoracic vertebræ. The spinal dura was involved on its outer anterolateral surface and the cord was displaced to the left. On opening the dura from behind there appeared to be no extension of the growth intradurally. There was local invasion by the growth in the vertebral laminæ, muscles, and the pleura and lung at the right apex; the posterior and inner cords of the brachial plexus were also involved in the tumour mass.

Histology (fig. 6).—The tumour cells are large and mainly ovoid; they are densely packed with a brown pigment (melanin). The nucleus stains deeply with hæmatoxylin in most of the cells, but in many the structure of the cell is completely obscured by the pigment. It is impossible to obtain a clear picture of either cell or tissue architecture for this reason. The invasive character of the tumour is best seen in sections taken from the outlying portions of the growth (e.g., pleura) in which are isolated clumps of pigmented cells separated by a fibrous stroma. Pieces removed from the centre of the growth show areas of necrosis with a scattering of the pigment outside the degenerated cells.

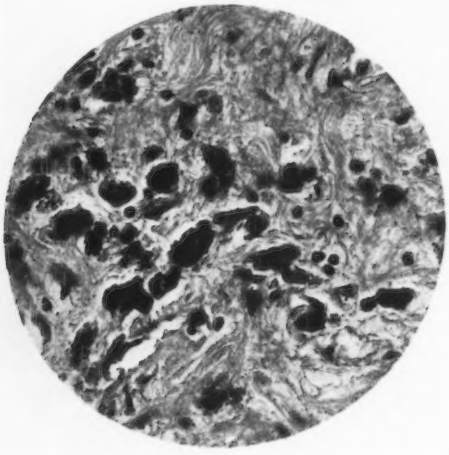

FIG. 6 (*Case* 2).—Section taken from the periphery of the growth (× 300).

This tumour may have arisen as an extradural spinal tumour growing out of the canal, or it may have arisen from without, possibly from the inferior cervical or first thoracic sympathetic ganglion which lies somewhere within the main mass of the tumour.

Case 3.—A. B., male, aged 21, was seen January 14, 1931. He had complained of weakness and numbness of both lower limbs and of the left arm for six months. For three years he suffered from "rheumatic" pain radiating from the left shoulder down the outer side of the arm; gradually weakness of the left arm developed, and six months ago numbness in the right leg with an inability to appreciate cold water over the right leg; gradually progressive difficulty in walking appeared.

On examination there was evidence of compression at level of seventh cervical and first dorsal segments of the cord, affecting the left side. Cerebrospinal manometry showed evidence of partial obstruction. The cerebrospinal

fluid contained a slight excess of protein, but no other change. X-ray of the cervical and dorsal spines revealed no abnormality. The Wassermann reaction in the blood was negative.

Operation (25.1.31) by Professor R. E. Kelly. On incising the dura, a tumour 1 × ½ inch presented on the left side of the cord underlying the posterior root of the sixth cervical nerve which was cut to facilitate its removal; on raising the tumour it was found to extend along the intervertebral foramen, and this necessitated removal of more bone and dura; then the tumour was found to be passing outside the spine. After its removal by morcellement the bed of the tumour was represented by a cavity about the

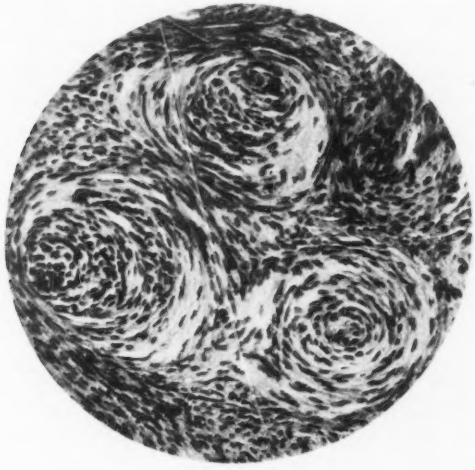

FIG. 7 (*Case* 3).—Section of the tumour (× 250).

size of a walnut extending outside the intervertebral foramen; this cavity was scraped and the area treated by coagulation with electrocautery.

Pathological report.—" Meningeal endothelioma of the cord " (fig. 7). The patient made a complete recovery, except for slight sensory disturbance in left upper limb which has persisted until the present.

SITE OF TUMOURS.

Any level of the spine may be implicated and these tumours may arise from any structure, nervous, fascial, osseous, &c. They may arise intraspinally and grow outwards through an intervertebral foramen or rarely between the laminæ, thus forming an extraspinal portion, or they may arise extraspinally and then extend through an intervertebral

foramen and form the intraspinal prolongation. The communicating narrowed isthmus gives the hour-glass or dumb-bell shape; usually the intervertebral foramen through which the tumour passes is enlarged by pressure atrophy; occasionally invasion and destruction of bone occur. It is customary to exclude from the group under discussion rapidly growing malignant tumours which cause gross vertebral destruction by direct infiltration and invade the cord secondarily.

Literature.

There is scant reference in the literature to these tumours. Heuer [1] in 1929 collected sixty-one cases from the literature, and added three personally observed cases and two personally communicated cases. Since then Gonzalez-Aguilar [2] has reported two round-celled sarcomas of the hour-glass type in the dorsal region, and Guleke [3] reports one cervical (chondroma) and one lumbar ("sympaticoblastoma").

In 1933 a further fifteen cases were added to the literature by Naffziger and Brown [4] bringing the total recorded cases up to eighty-five. Many of these have not been labelled hour-glass tumours, but the descriptions given in the records leave no doubt of their nature. They probably occur with far greater frequency than the literature indicates.

Pathology.

These tumours may arise from any tissue—the membranes, nerves, ganglia, sympathetic nervous system, ligaments, cartilage, bone, fat, &c.—but a very large number are fibroblastogenic or neurogenic and originate from the meninges, ganglia or nerve-roots. The great majority are benign encapsulated growths though a few are definitely malignant.

Pathogenesis.—Why these tumours should assume an hour-glass shape has been the subject of much discussion. If they arose primarily either intra- or extra-spinally, or even in the intervertebral foramen itself, and spread outwards or inwards, their shape could be explained, but it is difficult to understand why tumours originally extra- or intra-spinal should follow this line of growth except in the case of those arising from the nerve-sheath. Foyer discusses Coenen's view that these tumours are determined early in the course of development, and that they assume their hour-glass shape because other structures grow round and constrict them, the pathogenesis being similar to spina bifida occulta, dermoid cysts with both intra- and extra-cranial portions, intra- and extra-thoracic lipomata, &c.

Symptomatology.—The usual symptomatology of spinal compression with the accompanying changes in pressure and chemistry of the cerebrospinal fluid may be present, but additional features which merit emphasis are :—

(1) The frequent and severe root pain, resulting from the situation of the tumour.

(2) In the cervical region and occasionally in the lumbar region a palpable lump may be found : in the latter area, either in the back or on abdominal examination. Rarely except by X-ray examination is the extraspinal portion in a thoracic site discovered.

(3) Symptoms may arise from vertebral damage, i.e. pain on movement, rigidity, &c.

Diagnosis.—Acquaintance with the lesion is the prime essential for its recognition. Most cases, particularly those with vertebral damage demonstrated by X-ray examination, have been regarded as tuberculous disease of the spine with secondary abscess formation, an error only possible if an hour-glass tumour of the spine has not previously been seen by the physician or radiologist.

Treatment.—In order to prevent recurrence of the tumour, both intra- and extra-spinal portions must be removed. Many cases of recurrence of spinal tumours depend upon a non-recognition of the extraspinal portion in this type of case. Some surgeons advocate one, others a two-stage operation, but all seem agreed that the primary attack should be on the intraspinal portion. It is interesting to note that in the case of a thoracic situation the extraspinal portion has been so large that it has been removed without recognizing its hour-glass nature ; as a result, not only has compression paraplegia developed subsequently but injury to the spinal meninges has occurred during the removal of the extraspinal portion so that cerebrospinal fluid has leaked into the pleura and produced a hydrothorax.

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THE CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS.

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THE purpose of this article is to report the cerebrospinal fluid findings in 152 fluids from 100 cases of multiple sclerosis that have been under observation on the Neurological Services of the Boston City Hospital and the Massachusetts General Hospital during the past nine years and to summarize the reports in the literature on this subject.

I.—CEREBROSPINAL FLUID FINDINGS IN 100 CASES OF MULTIPLE SCLEROSIS.

The 100 cases here reported are all fairly typical cases. They have all been examined by several observers who have concurred in the diagnosis. All cases were excluded in which the diagnosis was doubtful, or in which there was a difference of opinion among various observers. The Wassermann test was done on the blood and cerebrospinal fluid, and was negative in every case.

Necropsy confirmation had been obtained in only one of the cases, but it is felt that the diagnosis is relatively certain in the remainder of the cases. In a disease with protean manifestations 100 per cent. accuracy of diagnosis is hardly possible, and it is likely that we have excluded some cases that would show the typical pathology, and on the other hand we may have included some in which the diagnosis would not be confirmed by necropsy. We have, however, tried to err on the side of conservatism.

(1) *Cerebrospinal fluid pressure.*—The cerebrospinal fluid pressure was measured 123 times in the 100 cases. Lumbar puncture was performed with the patient in the lateral recumbent position. The cerebrospinal fluid pressure was measured with the Fremont-Smith modification of the Ayer manometer. The pressures ranged between 40 and 220 mm., with an average of 131 mm. of cerebrospinal fluid pressure. In only one instance was the pressure more than 200 mm.

of cerebrospinal fluid. The dynamics of the cerebrospinal fluid circulation, as tested by compression of the jugular veins, &c., was normal in all instances. Table I gives an analysis of the pressure at 123 punctures.

TABLE I.—THE CEREBROSPINAL FLUID PRESSURE IN 100 CASES OF MULTIPLE SCLEROSIS (123 PUNCTURES).

Cerebrospinal fluid pressure (in mm. of C.S.F.)	Number of punctures	Percentage
Under 80	15	12
81-150	78	63
151-180	24	20
181-200	5	4
201-220	1	1
	123	100

(2) *Cells.*—The cells in the spinal fluid were counted in ordinary blood-counting chambers, the cells being faintly stained with Unna's polychrome methylene blue (methylthionine chloride, U.S.P.) The cell-counts varied between 0 and 40 per c.mm., with an average of 6 per c.mm. Table II gives an analysis of the findings in the 141 fluids in which the cells were counted.

TABLE II.—ANALYSIS OF THE CELL COUNT IN 141 FLUIDS.

Cells per c.mm.	Number of cases	Number of fluids
Not counted	4	—
0	8	18
1-5	54	79
6-10	14	20
11-20	12	14
21-40	8	10
Total	100	141

Sixty-nine per cent. of the 141 fluids in which the cells were counted had less than six cells per c.mm. and 31 per cent. had six or more cells per c.mm. More than ten cells per c.mm. were found in 18 per cent. The cells were chiefly small lymphocytes. Occasionally small mononuclear cells were found. Polymorphonuclear leucocytes were not found.

(3) *Protein content.*—The protein content was determined in 151 fluids from 100 cases according to Ayer, Dailey and Fremont-Smith [1] modification of the Denis and Denis and Ayer method. Their figure of 45 mg. per 100 c.c. is considered as the upper limit of normal values. Our results varied between 13 mg. and 133 mg., with an average of 43 mg. per 100 c.c. The protein content was over 100 mg. in only three cases (4 fluids). Sixty-eight per cent. of the fluids showed a total protein content within normal limits. Forty per cent. of the fluids

with a normal protein had a protein content between 36 to 45 m.g., i.e. high normal values. Thirty-two per cent. of the fluids showed an increase in the total protein content. In 9 per cent. of the fluids, the protein content was over 75 mg. per 100 c.c. Table III gives a summary of the findings.

TABLE III.—ANALYSIS OF THE PROTEIN CONTENT IN 151 FLUIDS.

Protein mg. per 100 c.c.	Number of cases	Number of fluids
Less than 20 ..	5 ..	7
21-35 ..	32 ..	55
36-45 ..	25 ..	40
46-75 ..	28 ..	36
76-100 ..	7 ..	9
Over 100 ..	3 ..	4
	100 ..	151

A qualitative globulin test was done in 75 fluids and was positive in 38 instances or 51 per cent. The Pandy test for globulin was done in 52 fluids and was positive 31 times. The test was usually only slightly positive. The total protein content was normal in 18 of the 31 fluids giving a positive Pandy test. The Ross-Jones test for globulin was done in 35 fluids and was positive 8 times. The total protein content was normal in 3 of these 8 fluids.

(4) *Sugar content.*—The reducing substances were determined in 31 fluids by the Folin-Wu method as modified by Rothberg and Evans [2]. The results varied between 51 and 78 mg. per 100 c.c. with an average of 66 mg. per 100 c.c. (normal values 45 to 93 mg. per 100 c.c. [3].

(5) *Chloride content.*—The chloride content was determined in 26 fluids by the Wilson-Ball [4] modification of the Van Slyke method. The results (expressed in mg. of NaCl per 100 c.c.) varied from 684 to 754 mg. with an average of 724 mg. per 100 c.c. In only one fluid was the chloride content below 695 mg. per 100 c.c. (normal values 695 to 750 mg. per 100 c.c. [3]).

(6) *Non-protein nitrogen.*—The non-protein nitrogen was determined in 8 fluids by the Folin-Wu [5] method. The results varied from 13 to 28 mg. with an average of 17 mg. per 100 c.c. (normal values 12 to 28 mg. per 100 c.c. [3]).

(7) *Colloidal gold reaction.*—The colloidal gold reaction was done according to the method of Lange as described by Cockrill [6] in 142 fluids (Table IV). The results varied from a strong first zone curve ("paretic") to an entirely negative test. The expression "strong curve" is used to represent one in which certain tubes showed a complete

decolorization, 5, or a blue colour, 4. "Weak curves" mean those curves in which the maximum colour change is violet, 3. Where the maximum colour change was lilac, 2, the fluid was classified as slightly abnormal. Any change in the colloidal gold solution of a lesser degree was considered as normal.

TABLE IV.—ANALYSIS OF THE COLLOIDAL GOLD REACTION ON 142 FLUIDS.

	Number of cases	Number of fluids	Percentage of fluids
Strong first zone curve ..	23 ..	38 ..	27
Weak	6 ..	8 ..	6
Strong mid-zone curve ..	4 ..	4 ..	3
Weak	17 ..	20 ..	14
Slightly abnormal curve ..	23 ..	36 ..	25
Normal	24 ..	36 ..	25
Not done	3 ..	— ..	—
	100 ..	142 ..	100

Thirty-three per cent. of the fluids gave a first zone curve, 27 per cent. of which were strong, 6 per cent. weak. Seventeen per cent. of the fluids gave a mid-zone curve of which 3 per cent. were strong and 14 per cent. were weak. In 25 per cent. the gold curve was only slightly abnormal (lilac colour change) and in 25 per cent. the curve was normal.

(8) *Calcium.*—The calcium content of the serum and the cerebrospinal fluid was determined in 15 cases by the method of Fiske and Logan [7]. In all cases the cerebrospinal fluid calcium was between 47 and 55 per cent. of the blood calcium level. The actual range of figures was 4·2 to 5·0 mg. with an average of 4·8 mg. for the cerebrospinal fluid and 9·3 to 10 mg. with an average of 9·6 mg. per 100 c.c. for the serum calcium content. (Normal cerebrospinal fluid values 4·1 to 5·9 mg. per 100 c.c. [3]).

(9) *Phosphorus.*—The inorganic phosphorus content of the serum and cerebrospinal fluids was determined in 7 cases by the method of Fiske and Subbarow [8]. The cerebrospinal fluid content results varied between 1·2 and 1·6 mg. with an average of 1·4 mg. per 100 c.c. The serum phosphorus content varied between 2·9 and 4·5 mg. with an average of 3·8 mg. per 100 c.c. (normal values for cerebrospinal fluid 1·2 to 2 mg. per 100 c.c. [3]).

(10) *Sodium.*—The sodium content was determined in 12 fluids by the Rourke [9] modification of the Kramer-Gittleman method. Our results varied from 297 to 343 mg. with an average of 326 mg. per 100 c.c. (normal values 297 to 348 mg. per 100 c.c. [3]).

(11) *Total solids.*—The total solids of the cerebrospinal fluids were determined in 18 fluids by drying to a constant weight at from 105° to 110° C. The results varied from 0·85 to 1·21 per cent. with an average of 1·0 per cent. (Normal values 0·85 to 1·70 per cent. [3]).

(12) *Freezing point.*—The freezing point was determined in 9 cases by the method of Beckmann [10], a Heidenhain thermometer being used. The results varied between − 0·540° C. and − 0·580° C. with an average of − 0·572° C. (Normal values − 0·540° C. to − 603° C. [3]).

Discussion.

From our findings it appears that abnormalities in the cerebrospinal fluid in multiple sclerosis are almost entirely limited to an increase in cells, an increase in protein, and changes in the colloidal gold reaction. The pressure, hydro-dynamics, sugar, non-protein nitrogen, chlorides, sodium, calcium, phosphorus, total solid content and freezing point are nearly always normal.

The cerebrospinal fluid in this disease may vary from an entirely normal fluid to a fluid showing increase in cells up to 40 per c.mm., a positive globulin reaction, a total protein increase up to 133 mg. per 100 c.c. and a change in the colloidal gold reaction in the first or mid-zone up to a strong "paretic curve." Abnormalities in one or two of these reactions is considerably more common than in all three.

If each individual test is considered it is seen that normal findings occurred in the following percentages: cells, 69 per cent; protein, 68 per cent.; and colloidal gold curve 25 per cent. If, however, the cases are analysed for all three tests it is apparent that only a very small percentage (17 per cent.) gave entirely normal findings. This is especially true when the patients had more than one lumbar puncture. In several cases the fluid obtained on subsequent punctures showed variations from the findings at the first puncture. In this connection it is of interest that Fremont-Smith, Putnam and Cobb [11] found that the cell-count and protein content of the cerebrospinal fluid from cases of multiple sclerosis occasionally showed a marked increase during "forced drainage."

Table V shows the relative incidence of the abnormalities in cell-count, protein content, and colloidal gold reaction in our cases. In the cases which had two or more punctures a composite of all the fluids was used in determining the percentages of abnormalities. The fluids were entirely normal in only 17 cases. One abnormality was present in 37 cases and more than one abnormality was present in 46 cases. An

abnormality in all three, i.e. pleocytosis, increased protein and an abnormal gold curve was found in only 14 cases.

TABLE V.—RELATIVE FREQUENCY OF ABNORMALITIES IN THE CEREBROSPINAL FLUID.

	Number of cases
All fluids normal	17
Pleocytosis only	1
Increased total protein only	7
Slightly abnormal gold curve only	13
First zone or mid-zone gold curve only	16
Abnormalities in two tests	32
Abnormalities in all three tests..	14
Total	100

The presence of a strong zone I (paretic) colloidal gold curve in 13 fluids which had neither a pleocytosis nor abnormal protein content shows that this reaction is not dependent on either of these two constituents. Our data also shows that a normal or only slightly abnormal colloidal gold reaction may be found in cases with a high protein content. Nine of the 13 fluids with a protein content greater than 75 mg. had a normal or only slightly abnormal gold curve.

An entirely normal gold curve was not found in any of the fluids with more than 10 cells per c.mm. There were 24 fluids with more than 10 cells per c.mm., 11 showed a zone I, 8 a mid-zone and 5 a slightly abnormal colloidal gold curve. A marked change in the colloidal gold curve (zone I or mid-zone) was therefore found in only 31 per cent. of the fluids with a protein content greater than 75 mg. per 100 c.c. as compared to 79 per cent. of the fluids with more than 10 cells per c.mm.

There was no definite relationship between the cell count and protein content of the fluids. Fourteen (60 per cent.) of the 24 fluids with more than 10 cells per c.mm. had normal protein content. Only one of the 13 fluids with a protein content greater than 75 mg. had a cell-count greater than 5 per c.mm., and in none of these fluids was the cell-count greater than 10 per c.mm.

THE RELATIONSHIP OF THE CEREBROSPINAL FLUID FINDINGS TO THE CLINICAL COURSE.

In a disease such as multiple sclerosis it is impossible definitely to divide the cases into progressive and stationary ones; cases presenting new symptoms are easily classified but it is very difficult to determine from the records whether old symptoms are progressing. It is questionable, therefore, if such an analysis will yield reliable results. Neverthe-

less, we have attempted to divide the cases into two groups: progressive and stationary. In the latter group we placed all the cases that have had no new symptom for one year, and in whom there had been no definite progression of the old symptoms within the year previous to the lumbar puncture. All other cases are, for the purpose of comparison, classified as progressive, although in eight cases the patients were under observation too short an interval after their initial attack to classify them satisfactorily.

With the above criteria 18 of the 100 cases could be classed as stationary. Tables VI, VII and VIII present a comparison of the findings in the fluids on the progressive and stationary cases.

TABLE VI.—COMPARISON OF THE CELL COUNT IN THE FLUIDS FROM PROGRESSIVE AND STATIONARY CASES.

	Progressive		Stationary		Total	
Cells per c.mm.	Number fluids	Per cent.	Number fluids	Per cent.	Number fluids	Per cent.
Less than 6 ..	75	64	22	92	97	69
6-10 ..	18	16	2	8	20	14
Over 10 ..	24	20	0	0	24	17
	117	100	24	100	141	100

TABLE VII.—COMPARISON OF THE PROTEIN CONTENT IN THE FLUIDS FROM PROGRESSIVE AND STATIONARY CASES.

	Progressive		Stationary		Total	
Protein mg./100 c.c.	Number fluids	Per cent.	Number fluids	Per cent.	Number fluids	Per cent.
Normal ..	82	66	20	77	102	68
Over 45 ..	43	34	6	23	49	32
	125	100	26	100	151	100

TABLE VIII.—COMPARISON OF THE COLLOIDAL GOLD CURVE IN THE FLUIDS FROM PROGRESSIVE AND STATIONARY CASES.

	Progressive		Stationary		Total	
	Number fluids	Per cent.	Number fluids	Per cent.	Number fluids	Per cent.
Normal	22	19	14	58	36	25
Slightly abnormal	31	26	5	21	36	25
Zone I curve ..	43	36	3	13	46	33
Mid-zone curve ..	22	19	2	8	24	17
	118	100	24	100	142	100

While it was found that a normal or almost normal fluid could be present in a case showing new symptoms or progression of old symptoms, and also that a definitely abnormal fluid could be present in a stationary case, there was a much higher percentage of abnormal findings in the progressive cases, as shown in Table IX.

TABLE IX.—SUMMARY OF THE COMPARISON OF THE PERCENTAGE OF ABNORMAL FINDINGS IN THE PROGRESSIVE AND STATIONARY CASES.

	Progressive cases	Stationary cases
Pleocytosis more than 5 per c.mm. ..	36 per cent.	8 per cent.
Pleocytosis more than 10 per c.mm. ..	20 ,,	0 ,,
Protein more than 45 mg. per 100 c.c. ..	34 ,,	23 ,,
Abnormal colloidal gold—		
Zone I curve	36 ,,	13 ,,
Zone II curve	19 ,,	8 ,,

Two significant facts were brought out by the analysis of our cases: (1) All of the 24 fluids with a pleocytosis of over 10 cells per c.mm. were in the progressive cases. This is in accord with the findings of Ayer and Foster [12*a*]. Their 8 cases with a like grade of pleocytosis were progressive ones. (2) Table V indicates that 14 cases showed an abnormality in the cell-count, protein content and colloidal gold test. Twelve of these cases were progressive and the two remaining were early cases.

II.—SUMMARY OF THE CASES REPORTED IN THE LITERATURE.

Table X gives a summary of the cerebrospinal fluid findings in 1,068 cases of multiple sclerosis that are recorded in the literature [12]. Our 100 cases are included in this table.

(1) *Pressure.*—There is very little in the literature with regard to cerebrospinal fluid pressure in multiple sclerosis. Most authors state that it is generally normal. Ayer [12*a*] found the pressure normal in all of his 38 cases. Greenfield and Carmichael [12*e*] state that the pressure is commonly raised but is never over 200 mm. of cerebrospinal fluid. Guillain [12*f*] found the pressure elevated in 5 of his 14 cases. In our series the average pressure was 131 mm. of cerebrospinal fluid The highest pressure recorded was 220 mm.

(2) *Cells.*—In the 986 fluids in which the cell-counts were recorded, 283 fluids or 28 per cent. showed a pleocytosis. It is agreed by most authors that 5 cells per c.mm. is the upper limit of normal and this figure was used in computing these cases whenever the data were sufficient to permit. Pleocytosis when found was generally of only a moderate degree. In the greater majority of the cases it was under 10. Greenfield and Carmichael [12*e*] report one case with 115 cells and Moore [12*h*] found 89 cells in one case, but such counts are exceptional. The upper limit of most other observers was 40 to 50 cells per c.mm.

(3) *Protein content.*—(*a*) Qualitative: In 825 qualitative tests the protein content (usually globulin) was abnormal in 374 or 45 per cent.

TABLE X.—THE CEREBROSPINAL FLUID FINDINGS IN 1,068 CASES OF MULTIPLE SCLEROSIS.

AUTHOR	Number of cases	CELLS		PROTEIN				COLLOIDAL GOLD				
				Qualitative		Quantitative						
		Number of counts	Number with increase	Number of tests	Number with increase	Number of tests	Number with increase	Number of tests	First zone	Mid-zone	Other forms	Neg.
Ayer	38	51	19	31	9	38	19	42	21	7	3	11
Beriel	47	47	11	—	—	—	—	—	—	—	—	—
Conoway	10	10	4	10	3	—	—	10	2	3	—	5
Eskuchen	41	41	21	41	28	—	—	41	10	17	—	14
Greenfield and Carmichael	250	250	30	250	86	250	29	190	27	37	113	13
Guillain	27	27	1	—	—	27	8	27*	1	2	14	10
Kaplan	18	—	—	—	—	—	—	18	1	—	—	17
Moore	28	28	16	28	25	—	—	28	18	3	—	7
Müller	100	100	27	100	49	100	33	47	7	19	—	21
Potts	35	—	—	—	—	—	—	35	11	4	10	10
Reys	67	67	28	67	21	—	—	—	—	—	—	—
Rogers	65	—	—	—	—	—	—	65	17	4	19	25
Sternberg	126	108	67	126	94	—	—	83	26	34	2	21
Warwick	19	19	6	—	—	—	—	19	5	2	2	10
Wexberg	82	82	9	82	19	—	—	77	16	20	—	41
Worster-Drought	15	15	—	15	2	—	—	15	1	12	—	2
Personal Cases	100	141	44	75	38	151	49	142	46	24	36	36
TOTAL	1,068	986	283	825	374	566	138	839	209	188	199	243
Per cent. abnormal	—	—	28%	—	45%	—	24%	—	25%	22%	24%	—

* Colloidal benzoin test.

The various tests used were generally reported as being weakly or only moderately positive.

(*b*) Quantitative: The percentage of cases showing a quantitatively increased protein content was somewhat less than that of the qualitative test. Of the 566 quantitative tests, 138 or 24 per cent. showed an increase above the arbitrary normal limit. A large percentage of the remaining fluids were stated to have high normal protein values. The protein content of the fluids varied between 150 and 13 mg. In only three of our cases was the protein over 100 mg. Greenfield and Carmichael [12*e*] found a total protein over 100 mg. in only one case.

(4) *Colloidal gold test.*—This test has received the most attention in the literature as it is often the most striking finding in the fluid. It is also not infrequently the only abnormality found.

In the 839 fluids in which this test has been done 209 or 25 per cent. showed a first zone (paretic) curve; 188 or 22 per cent. showed a mid-zone (luetic) curve; 199 additional cases, 24 per cent., showed slight abnormalities (lilac in the mid-zone), or other variations from the normal. Thus in 596 cases or 71 per cent. the colloidal gold curve was abnormal.

With regard to the influence of the cells and protein content on the gold curve our results were in agreement with the statement of Greenfield and Carmichael [12*e*], that strong colloidal gold curves were more often associated with a high cell-count than a high total protein. In the 37 fluids in our series that had a protein content over 50 mg. only 15 (40 per cent.) had an abnormal gold curve, whereas 19 (79 per cent.) of the 24 fluids that had over 10 cells per c.mm. showed a zone I or mid-zone colloidal gold curve.

(5) *Other constituents.*—There is little in the literature with regard to the other characteristics of the cerebrospinal fluid in multiple sclerosis. Kafka [13] has studied the physical characteristics of the fluid (interferometry, spectroscopsy, &c.). The only series of cases previously reported which has included a complete chemical examination of the fluid is that of Ayer and Foster [12*a*]. Their figures for the sugar, chlorides and non-protein nitrogen are in accord with our data. They examined the fluids also for creatinin content (4 cases, 1·2 to 2·38 mg. with average of 1·78 mg.), urea content (6 cases, to 0 – 24·3 mg., with an average of 15·5 mg.) and acetone (11 cases, none found).

Colloidal tests other than the colloidal gold have been studied [14]. The colloidal benzoin, mastic tests, &c., usually gave results less positive than the colloidal gold test.

(6) *Correlation between cerebrospinal fluid findings and the clinical course.*—Only few observers have made any effort to correlate the clinical course with the cerebrospinal fluid findings. They all agree that an entirely normal fluid may be found in acute or rapidly advancing cases, and a markedly abnormal fluid may be found in stationary cases. Our observations and those of Ayer and Foster [12*a*] would indicate that there is, however, a rough degree of correlation between the clinical course and the cerebrospinal fluid findings; the acute and progressive cases showing a much greater percentage of abnormalities than the stationary cases. Müller [12*i*] stated that the presence of a first zone (paretic) gold curve indicated that the course of the case would be one of remissions and exacerbations. Rogers [12*l*] felt that there was no definite relationship between the clinical course and the changes in the gold curve, and that there was no evidence that therapy produced any changes in the colloidal gold curve that might not occur spontaneously. Our results, as well as those of Ayer and Foster [12*a*], suggest that a pleocytosis greater than 10 cells per c.mm. indicates a progressive case. Our statistics also show that the combination of an abnormality in cells, protein and the colloidal gold test occurs only in progressive or early cases.

The occurrence of a positive Wassermann reaction in the cerebrospinal fluid is considered as excluding the diagnosis of multiple sclerosis.

Summary.

(1) The cerebrospinal fluid findings in 100 cases of multiple sclerosis are reported and findings in 968 previously reported cases are summarized.

(2) The cerebrospinal fluid is absolutely normal in less than 20 per cent. of the cases of multiple sclerosis.

(3) The intracranial pressure is usually normal, but may occasionally be very slightly elevated. A pressure greater than 200 mm. of cerebrospinal fluid is practically never found.

(4) Pleocytosis of a moderate grade (6 to 40 cells per c.mm.) is a frequent finding. It occurred in 28 per cent. of the recorded cases.

(5) A quantitative abnormality of the protein content of the fluid was present in 45 per cent. of the reported cases. A quantitative increase in the protein content above the arbitrary normal limit was present only in 24 per cent.

(6) An abnormal colloidal gold curve was present in 71 per cent. of the cases. These abnormalities were divided as follows :—

First zone curve	.. ..	25 per cent.
Mid-zone curve	.. ..	22 ,,
Other abnormalities	.. ..	24 ,,
Total	.. ..	71 per cent.

(7) The fluid is usually normal in regard to its chloride, glucose, non-protein nitrogen, calcium, phosphorus, sodium, total solid content and freezing point. The cerebrospinal fluid Wassermann is always negative.

(8) There is a rough degree of correlation between the clinical course and the cerebrospinal fluid findings. A higher percentage of abnormalities is found in the fluids of active cases than in the fluids of stationary cases. A pleocytosis of over 10 cells per c.mm., or an abnormality in cells, protein and colloidal gold all in the same case are found only in progressive cases.

(9) There are no changes in the cerebrospinal fluid that are pathognomonic of multiple sclerosis. The presence of a first or mid-zone colloidal gold curve with or without a slight pleocytosis and increased protein content, in an otherwise normal fluid, is supporting evidence for the diagnosis of multiple sclerosis in a clinically suspicious case. This is only true if there is no history of syphilis or anti-luetic treatment.

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THE SYNDROME OF THE PREMOTOR CORTEX IN MAN: IMPAIRMENT OF SKILLED MOVEMENTS, FORCED GRASPING, SPASTICITY, AND VASOMOTOR DISTURBANCE.

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THE symptom of forced grasping has long been recognized in man, but the physiological basis of this phenomenon is not yet clearly understood; nor has it been sufficiently appreciated that forced grasping is invariably associated with a number of other equally striking clinical signs which together form a well-defined clinical entity. The case herein described illustrates the syndrome in all its features, and is perhaps of greater significance from the point of view of localization than many previously reported cases of forced grasping, since the lesion proved to be a removable tumour restricted to the premotor area of the cerebral cortex (area 6 of Brodmann).

I.—PREVIOUS OBSERVATIONS.

As early as 1903 Steinert [23] reported a case of tumour of the left "paracentral lobule" (the premotor area) in which "tonic innervation" of the right arm was present. Since that time there have been many reports of clinical cases showing the same phenomenon. The pathological reflex status of these cases has been variously termed "tonic innervation" (Steinert [23], Liepmann [16], Wilson and Walshe [26]), "palmar reflex" (Riddoch and Brain [19]), "Greifereflex" (Schuster and Pinéas [22]), and "forced grasping" (Adie and Critchley [1]).

Clinical studies.—Perusal of the extensive literature of this subject indicates that the clinical picture usually depicted in case histories is surprisingly definite, despite uncertainty concerning both the site of the lesion and the nature of the phenomenon itself, whether "voluntary," "involuntary," "associated" or purely "reflex" in character. In all clear-cut cases of unilateral reflex grasping the following symptoms are

associated with it on the affected side: increase of tendon reflexes, spasticity, hemiparesis or awkwardness of the extremities, and, occasionally, an extensor Babinski response. In addition nearly every case reported shows some psychic changes such as are usually associated with frontal lobe lesions: emotional instability, changes of character, or confusion and slowing of mental activity. There is scant reference, however, to vasomotor disturbance in the affected extremities.

In cases in which verification has been possible at autopsy, the *site* of the lesion has most often been the posterior part of the frontal lobe, just anterior to the motor or Betz cell area (Adie and Critchley [1]; Walshe and Robertson [25]); some authors, however, found that lesions of the corpus callosum may also be associated with the phenomenon, and still others have found lesions of the basal ganglia (Gullotta [11]) in cases of well-marked grasping.

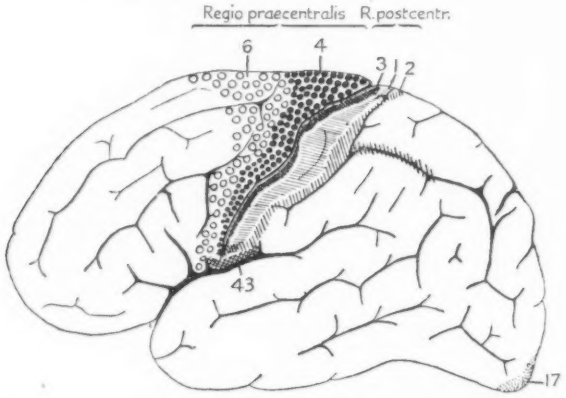

FIG. 1.—Left cerebral hemisphere in man, showing Area 6 (premotor area) and Area 4 (motor area). Reproduced from Brodmann's *Vergleichende Localisationslehre der Grosshirnrinde.*

Physiological studies.—In 1932 Richter and Hines [18] offered experimental evidence that a cortical lesion restricted to Brodmann's area 6 of the frontal lobe (fig. 1) produced involuntary grasping of the opposite extremity in rhesus monkeys. Later Fulton, Jacobsen and Kennard [9] by extirpation of the same area confirmed the findings of Richter and Hines concerning forced grasping, and in addition observed spasticity and increase in tendon reflexes on the side opposite to the lesion [15]. In these animals there was no evident alteration of behaviour. Further investigation of the problem by Bieber and

Fulton [2] demonstrated that the forced grasping resulting from a lesion of area 6 varies in intensity with the animal's position in space; they observed moreover that in monkeys from which the motor and premotor areas have been removed from both sides, the righting reflexes of Magnus and de Kleyn [17] are present, and they concluded that forced grasping is a part of the righting reflex mechanism peculiar to primates. It has also been found that lesions of area 6 cause temperature changes in the skin of the contralateral extremities (Fulton and Kennard [9], Kennard [14]).

II.—A Clinical Case.

These experiments indicate that reflex grasping may be caused in monkeys by a cortical lesion restricted to the premotor area. That this is also true in man is clear from the following case in which a lesion affecting the homologous area of the cortex (without extending deeply subcortically) produced a syndrome practically identical with that seen in monkeys, forced grasping, spasticity and increased tendon reflexes being present in the contralateral upper extremity. In addition the phenomenon of grasping was influenced by change of position of the body in space, and the skin temperature of the affected side was abnormal.

Case 1.—*Focal seizures, four years in duration, affecting left side of body, increasing rigidity, and awkwardness of left arm with forced grasping, increased reflexes and vasomotor disturbance; surgical removal of cystic glioma restricted to right premotor area; recovery with persistence of slight spasticity and grasping, and marked awkwardness.*

Charles H. S. (Case No. 329817), aged 34, a white American shoe salesman, entered the Massachusetts General Hospital, June 9, 1933, complaining of "fits."

Present illness—focal seizures.—Four years before admission an epileptiform attack occurred, said to have been generalized in character, which began in his sleep and lasted for about fifteen minutes. In this first attack the left arm was more affected than the other extremities. During the following month he had three or four similar attacks at night, but the details of these attacks were unknown since they always commenced in his sleep. A few weeks later he had his first attack during the day. While engaged in painting a sign he noticed that his head and eyes turned involuntarily to the left, and that his left arm, though rigid, was "shaking" and drawn up against his body. He then lost consciousness and fell. Since that time he had had seventy-five or a hundred similar attacks of varying intensity, often three or four occurring in a single day. In the few months before admission they had been more

frequent, and during the previous eight months he had noticed that the left leg was also involved both in the "shaking" and the sustained contraction. Individual attacks always began in the index finger of the left hand, and spread subsequently to the other fingers and to the wrist, arm, side of the face, and sometimes to the left leg. If the attack was going to be a severe one, with loss of consciousness, his head and eyes turned to the left side just before he became unconscious. He had developed the habit of holding the arm close against the body and of grasping his left hand, especially the index finger, with the right in order "to prevent the attack from coming on."

Since the onset of his illness there had been increasing awkwardness and stiffness of the left arm, and it had come to be impossible to use it for delicate manipulations, though there was still a powerful grip. For six months he had been conscious of inability to release the grasp of his left hand, and he had ceased making any attempt to use it because such effort was likely to bring on a seizure.

When his spells began, four years previously, he had considerable bilateral headache at the time of the attacks. More recently the headache had become less severe, and at times he had been quite free from it.

Within eight weeks of admission the patient had noticed that the left hand had become redder and warmer than the right hand. At times the hand was "swollen," a condition which was not constant, but occurred at irregular intervals, lasted for an hour or two and disappeared completely.

There had been no nausea or vomiting, and no visual disturbance: and at no time had his left extremities been completely paralysed.

Past history.—His general health had always been good, and the only illnesses reported were measles and mumps in childhood. There had been a small hæmorrhage from the left ear six months before entrance; the cause was not ascertained, but there were no after-effects. In 1917 he had been hit in the forehead with a baseball, with a short period of unconsciousness. There were no known sequelæ.

Physical examination (June 9, 1933).—His general physical examination revealed a fairly well-nourished young male with no abnormalities of significance apart from moderate ichthyosis of extremities and chest, chronic infection of the tonsils, and carious teeth without apical abscesses. His blood-pressure was 124/92.

Neurological examination.—The patient proved highly intelligent and co-operative. His olfaction, vision, visual fields and optic discs were normal. Abnormal findings were confined to the *left* half of the body. There was slight weakness of the left side of his face, particularly the lower half, involving the muscles around the corners of the mouth. The left arm was weak, especially in the grip, but there was no paralysis or atrophy.

Reflexes.—These were slightly greater in the left arm and leg, and there was a definite left ankle clonus, but plantar stimulation gave strong flexion of the toes.

Sensation: There were no gross sensory changes to touch. Stereognostic sense and two-point discrimination were normal.

Forced grasping: Any pressure on the flexor surface of the fingers of the left hand, particularly if it was sufficient to stretch the flexor tendons slightly, caused strong involuntary grasping. It was not induced by merely stroking the skin of the palm. With the appropriate stimulus, however, there was a slow involuntary flexion of the fingers, sometimes clonic and sometimes sustained in character. Relaxation was slow and apparently involuntary. This reflex grasping was augmented when the patient lay on his right side (the side of the presumed brain lesion) and lessened with the patient on his left side, although it was feebly present in this position.

Vasomotor changes: The left hand was redder and warmer than the right, and showed no œdema. There were no obvious thermal differences between the two legs.

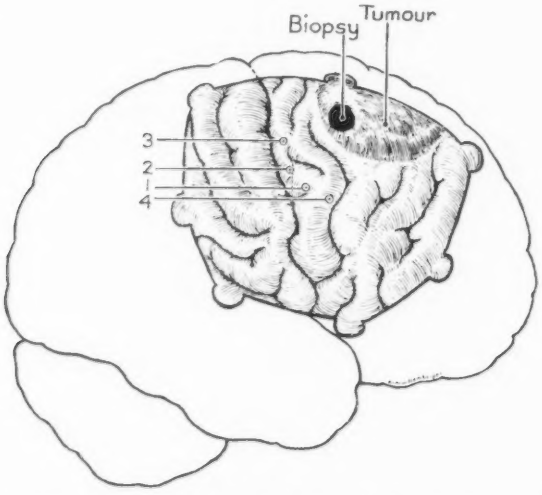

FIG. 2.—Reconstruction of the right cortex from cellophane tracing made at the first operation, showing site of tumour mass. Stimulation of Point 1 produced movements of the left forefinger; of Point 2 produced elbow movement; of Point 3 produced a Jacksonian attack; of Point 4 produced twitching of the left face followed by a Jacksonian attack.

Roentgenographic examination of skull: The size and shape of the sella turcica was within normal limits. There was no evidence of increased intracranial pressure. The pineal gland was not visible. No unusual areas of calcification were seen. There was an ill-defined area of slightly diminished density in the frontal bone just to the left of the midline. Running to this were two rather large blood-vessel grooves.

Laboratory reports.—The urine was normal in eight examinations. Blood (June 9): W.B.C. 4,700; R.B.C. 4,800,000; Hb. 90 per cent.; differential count normal. Lumbar puncture (June 9): Clear, colourless fluid; initial pressure 155 mm. of water, combined jugular compression 450, right jugular 290, left

jugular 300; pressure after withdrawing 5 c.c. 140; after withdrawing 10 c.c. 110; cells 0 per c.mm.; total protein 30 mgm. per 100 c.c.; gold sol 0000000000; Wassermann test negative.

First operation, June 19, 1933 (Dr. W. Jason Mixter).—Under local (novocain) anæsthesia a tripod incision was made in the right side of the scalp and a large bone flap turned down. The fissure of Rolando and the surrounding brain were thoroughly exposed. The dura was reflected upward, above the leg area, almost to the midline. Rather high up in the precentral region, apparently just anterior to the precentral gyrus, was an abnormal area of cortex about 3 cm. across, in which the sulci were absent (fig. 2). There were several large veins at the periphery, but almost none in this abnormal area, which was slightly purplish in colour, in contrast to the surrounding brain. This abnormal area had the appearance of an infiltrating glioma. It was possible that the edges represented gliosis about the tumour rather than the tumour itself. There was no increase in intracranial tension, and the area described, although slightly elevated above the surrounding brain, was not abnormal to touch. A piece was removed for examination.

Stimulation of the cortex.—Monopolar faradic stimulation was carried out at four points, just posterior to the mass and apparently in the precentral gyrus (fig. 2). The strength of current used, the weakest available, was probably too strong for discrete localization. On stimulating point 1 in the motor arm area, anterior to the fissure of Rolando, movements of the left forefinger were noted. Stimulation of point 2 gave elbow movement; stimulation of point 3 produced a Jacksonian attack, which started in the forefinger and spread to the hand, arm, face and leg on the left side. This lasted about fifty seconds. After the attack a small subpial hæmorrhage was seen over the tumour. In about ten minutes the cortex was again stimulated at point 4, probably in the face area of the motor cortex. This produced an immediate twitching of the head and face, followed in about sixty seconds by twitching of the left hand and in about a minute and a half by twitching of the left leg. All four extremities then became involved, and the attack lasted about one minute longer.

The diagram (fig. 2) was reconstructed from a tracing of the sulci and blood-vessels made on cellophane at the time of the operation. The tumour was outlined with ink. The points stimulated were placed upon a reconstruction made from the cellophane tracing.

Pathological report (Dr. Charles S. Kubik).—*Biopsy*: A small fragment of soft red tissue, examined microscopically, showed tumour tissue with many bipolar cells and fibrous glia. The pathological diagnosis was glioma, probably astrocytoma (see below). The total protein of the cystic fluid was 5,460 mg. per 100 c.c.

Post-operative notes.—For a few days after operation the patient's left hand was completely flaccid, with disappearance of forced grasping. The Babinski response became positive. Power and forced grasping returned after a week, and there were no Jacksonian attacks. A second operation was performed three weeks after the first.

Second operation, July 7, 1933 (Dr. W. Jason Mixter).—The old incision was reopened and the tumour exposed as before. Bone was cut away at the upper edge of the flap to give wider exposure, and the dura reflected almost to the longitudinal sinus. The pial veins running from the region of the longitudinal sinus were clipped and cut. Mass silk sutures were placed in the brain around the tumour. The tumour was then dissected out, leaving a margin of fairly normal brain tissue, the dissection approaching very closely to the precentral gyrus, presumably in the arm area. On making this dissection, a good-sized cyst containing yellowish fluid was found beneath the tumour with a mural nodule of tumour tissue projecting into the cyst. No attempt was made to dissect the whole wall of the cyst; all tumour tissue was apparently removed.

Pathological report of tumour and cyst (Dr. Charles S. Kubik).—A mass of tissue of firm and somewhat rubber-like consistency, measuring 5·5 by 4 by 1 cm. and weighing 16 grm., was examined. One surface was reddish in colour and covered with a thin, transparent membrane, containing fair-sized blood-vessels and resembling pia-arachnoid. The other surface was opaque and white in colour, smooth and glistening; in one part of it there was a slight elevation, 1·5 cm. in diameter, consisting of hæmorrhagic, soft, necrotic tissue. Incisions in various parts of the specimen revealed a pale, homogeneous cut surface. The microscopical appearance was similar to that seen in the previous biopsy, that is, areas of dense fibrous glia and bipolar cells and other more cellular areas with very little fibrous glia. Some fairly well-formed astrocytes were noted. Pathological diagnosis: Astrocytoma.

Post-operative notes.—First day: The patient was sitting up in bed, talking freely, and had practically no post-operative symptoms. There was complete flaccid paralysis of the left arm, so that the grasp reflex could not be tested. He had had no Jacksonian attacks since the operation, a period of twenty-four hours.

Fifth day: The patient showed no abnormal mental symptoms and was very co-operative; he was a little emotional but otherwise norma There was a well-marked left facial paralysis, central in type, and deviation of the tongue to the left. In the left arm there was no voluntary movement in the fingers, wrist, elbow or shoulder, and no sensory change to touch, but the sense of position in the fingers seemed slightly impaired. The abdominal reflexes were equal and active. There was some general weakness of the left leg, but all movements were possible. Sensation to touch appeared normal, but the sense of position of the big toe was impaired. The knee-jerks were equal, but difficult to obtain. Ankle clonus was easily obtained on the left. There were normal plantar responses on both sides.

Twelfth day: The patient had an attack of gross, jerky movements of the left side, beginning in the fingers of the left hand and extending up the arm to the side of the neck and into the face. The left side of the face was drawn up in the same gross movements. There was no loss of consciousness.

Thirteenth day: Flaccid paralysis of the left arm was still present and was most marked in the fingers and hand. The arm could be slightly flexed at the elbow voluntarily. Power in the left leg had become nearly normal.

Nineteenth day: The patient had another attack in the left arm, which again began with stiffness of the hand, followed by shaking in the shoulder, spasms of the side of the face, and some stiffness of the leg. There was no loss of consciousness and the patient considered it one of his lighter attacks. At this time power of the left arm was increasing daily and he could now raise the arm above his head. The fingers and wrist still showed complete paralysis.

Twenty-fifth day: The patient was discharged from the hospital. The decompressed area beneath the right temporal muscle was not distended. The left side of the face, around the corner of the mouth, showed a well-marked emotional type of paralysis, with some weakness on attempting to show the teeth. The left arm was somewhat stiffer than the right, with more active deep reflexes and a moderate degree of spasticity, but no loss of sensation. There was sometimes considerable trembling of the whole limb on attempted movement, not exactly of the intention tremor type, but a coarser, more rhythmic tremor. Power at the shoulder and elbow were almost normal. The wrist could be voluntarily extended to a point slightly beyond the midline. The fingers showed less power of extension, although all except the thumb were moved slightly. Voluntary flexion was better, although the hand could not be closed when the wrist was acutely flexed. Much of the power in the hand had reappeared in the preceding forty-eight hours. The left leg showed no paralysis, all movements being possible. There was slight weakness, however, at the ankle and the leg was somewhat stiffer than the right. The deep reflexes were increased and there was an easily elicited ankle clonus. The plantar reflex was plantar flexor. There was no loss of sensation in the leg.

Forced grasping: While lying on his back there was a moderately well-marked and easily elicited "grasping reflex" in the left hand when the palm was stroked from the wrist to the base of the fingers. Most of this reflex occurred in the fingers themselves, which were curled up in a position of 50-degree flexion and could not be relaxed. The reflex was more easily stimulated when the palm was stroked slowly. It did not appear to extend into the elbow or the shoulder. When the head was rotated sharply either to the right or to the left there was no change in this grasping reflex. However, when the patient turned his whole body to the right so that he was lying on his side, the reflex was increased very markedly in strength, so that the fingers were pulled away from the palm with considerable difficulty. When the patient turned on his left side, the reflex was somewhat diminished, but was practically the same as when he was lying on his back. The abdominal reflexes were present in all four quadrants, very easily elicited on the right side and fairly easily on the left.

The patient was cheerful and mentally active, taking a great interest in the examination. There were no signs of mental deterioration.

Twelve weeks (October 1, 1933): The patient was seen (by H. R. V.) at his home. He was up and dressed, walked, and seemed perfectly normal in his attitude and movements. He gave the following history of events since he

left the hospital: Early in August he had two slight attacks in his left arm, consisting of clonic movements, largely at the elbow, without movements of the fingers. There was no unconsciousness. Following this he was perfectly well for eight weeks, during which time he had been out nearly every day, and for a period of a day or two served as a shoe-store clerk He had no difficulty in doing the work except that his left hand was a little awkward in tying up shoestrings. There was no stiffness of the fingers and no tendency towards spasm or shaking. His hand was a little clumsy in feeding himself and fastening his clothes, but he was able to carry out all the usual movements without any marked difficulty. On September 28 he had a severe attack.

Other symptoms during the preceding two months had been as follows: He had not had headache, but there had been some neuralgic pains across his forehead. His eyes got a little tired and occasionally he had blurred vision. For some weeks his left hand had felt a little stiff. This had now entirely disappeared except possibly in the middle finger. He thought the grasping which he noticed before the operation, which was then so marked that he had difficulty in letting go of his clothes in attempting to put them on, had disappeared. There had been some swelling of the hand, from time to time, but this was no longer noticeable. The hand usually felt hot, but never cold. At times he thought it a little redder than that of the right side.

Examination (October 1, 1933): The scar was nearly healed and the bones not elevated. There was possibly a little weakness of the left side of the face, particularly around the corner of the mouth, but this was not very evident and was only observed at times. The left arm was somewhat atrophied throughout, particularly in the shoulder and upper part. Voluntary power, however, was present in all muscle groups. There was no paralysis and all movements were easily performed. The posture of the muscles seemed essentially normal. Deep reflexes, however, at the elbow and wrist were increased on the left side and Hoffmann's sign was present. The knee-jerks were equal. There was no disturbance of gait. There was no loss of sense of touch.

Forced grasping: This was still present in the left hand, being particularly evident when the patient lay on his right ride. Stroking the palm caused the fingers to be flexed so that they were straightened out with considerable difficulty. When the patient lay on his back, this reflex was still present, although much less, and when he lay on his left side there was no evidence of the reflex being present at all.

Thirteen weeks (October 7, 1933): The patient was seen in the Out-patient department of the Massachusetts General Hospital (by H.R.V. and J.F.F.). He reported no change in his condition since last seen, but the additional information was obtained that, prior to the appearance of motor disability in the left arm, the patient had noted that this extremity had seemed warmer and had sweated more. Since operation the left hand had been markedly warmer than the right and his left hand, arm, ear and face had been given to profuse sweating. For a time the left hand had been œdematous.

Examination revealed exaggerated reflexes in the left upper extremity, i.e., biceps, triceps and radial, and a Hoffmann's reflex was elicitable from the the tip of each digit. The abdominal reflexes were weaker on the left than on the right, but the knee-jerks and ankle-jerks appeared equal. There was an exaggerated plantar flexion on the left.

Forced grasping was also observed; very gentle contact with the skin of the palm did not in itself evoke grasping with the body in any position, but contact with the palm or skin at the base of the digits, especially when the patient's attention was diverted, caused a fairly prompt, involuntary grasp, which became exaggerated as one pulled slightly on the flexor tendons. This response was definitely more exaggerated when the patient lay on his right side but became greatly diminished and sometimes could not be elicited when the patient was on his left. With a little effort, even when lying on the right side, the patient could relax his grasp, but there was sometimes a considerable interval between command and execution of the extensor movement. Motor performance was normal apart from evident awkwardness in using the left fingers, as in dressing and undressing. Large objects could be picked up effectively with his left hand, but small objects were much less successfully manipulated. There was no disturbance in gait. Vasomotor disturbance was obvious in the left hand and forearm, which were pinker than the right. There was no œdema. There was no difference in colour or temperature of the two lower extremities, but the left ear was much redder than the right. Moisture of the left hand was greater than that of the right. The eye-grounds and extra-ocular movements were normal. There was slight weakness of the left corner of the mouth. The patient continued to be unaware of reflex grasping in the left hand with ordinary motor performance.

Subsequent history.—The patient reported (November 14) that motor power was improving and that involuntary grasping had become much less troublesome since he was last seen. Seven months after his operation (February 10, 1934) his condition remained relatively unchanged. There had been two Jacksonian attacks in the last three months. Forced grasping was only feebly elicited.

III.—Discussion.

The premotor syndrome, which this case and many others in the literature [1, 8, 11, 22, 25] so well illustrate, is characterized, when fully developed, by four distinctive symptoms which generally appear in definite chronological sequence: (i) inability to perform skilled movements, particularly with the digits, without gross impairment of motor power; (ii) spasticity with marked increase of deep reflexes, especially of the digits (sign of Hoffmann); (iii) forced grasping which may be influenced by the position of the body in space; (iv) vasomotor disturbances varying in degree from a slight alteration of temperature to states of marked œdema and hyperhydrosis.

The presence of Jacksonian seizures, spasticity, weakness and increase of reflexes, would not in themselves suffice to distinguish a motor from a premotor lesion of the cortex, for in cases of long-standing motor area lesions generalized weakness and Jacksonian seizures are also prominent symptoms, deep reflexes are likely to be increased, and spasticity may appear late. Foerster and Penfield [7] have pointed out, however, that the Jacksonian seizures produced by premotor lesions (Area 6aβ) tend to be adversive in type, i.e. beginning by turning of the head as in this case, whereas sharply focal seizures beginning in a single muscle denote a lesion nearer the central sulcus, i.e., in Area 4 or the caudal part of Area 6a a.

Chronology of symptoms in premotor lesions.—Forced grasping, and probably also vasomotor disturbances, are likely to appear late in the history of cases with premotor lesions, and it should be possible by a careful study of the chronology of symptoms to establish a localizing diagnosis before forced grasping appears. Gradually increasing awkwardness in an extremity, affecting more particularly highly integrated digital movements, such as those involved in sewing, piano playing, buttoning a shirt, in itself suggests a premotor lesion, provided the awkwardness is not accompanied by tremor, resting or intentional. Jacksonian attacks may or may not occur, but spasticity and the increase in tendon reflexes develop early. The grip and other gross movements of the extremity do not become seriously impaired until the awkwardness, spasticity and forced grasping are fully developed.

Chronology of symptoms in motor area lesions.—In gradually expanding lesions of the motor area, on the other hand, generalized weakness of the extremity, especially of the grip, appears precociously, there is no forced grasping, and spasticity, if present at all, appears late. Acute injuries (as in the above case after the second operation), or rapidly expanding lesions of the motor area, produce flaccid paralysis and generalized depression of the reflexes.

We may now discuss the individual symptoms of the premotor syndrome in relation to the corresponding symptoms observed in monkeys and apes after premotor lesions [9, 14, 15].

Experimental destruction of the premotor area in a monkey or chimpanzee reproduces the premotor syndrome in its fully developed state, i.e. marked vasomotor disturbance, forced grasping, spasticity and failure of every type of skilled movement, and it is highly significant that during the period of recovery from such an experimental lesion the symptoms to disappear first (forced grasping and vasomotor

disturbance [14, 15]) are those which appear latest in the clinical premotor syndrome; while the symptoms which persist longest following the experimental lesions (impairment of skilled movements and increase of reflexes [14, 15]) are those which appear first in the clinical anamnesis. The precocious disturbance of skilled movements may therefore be regarded as the most significant feature of the premotor syndrome.

(1) *Impairment of skilled movements.*—Appearing first in clinical cases and persisting longest in experimental animals, the disturbance of acquired skilled movements may be looked upon as the primary symptom of lesions of the premotor area. This is not a new conception in clinical neurology, for the premotor region has, since the work of Campbell [4] in 1905, or possibly earlier, been looked upon as the part of the brain in which "motion formulæ for skilled acts are constructed and retained" (Tilney and Riley [24]); but the experimental analysis and proof of the correctness of this inference is new and deserves brief mention. In a series of monkeys and chimpanzees trained to perform complex manipulations ("problem boxes"), Jacobsen [12, 13] has shown that following removal of the premotor area, gross impairment of all forms of skilled movement still persists after forced grasping and spasticity have passed off as demonstrated by the animal's reluctance to use the affected extremity, and its awkwardness in carrying out any manipulations requiring delicate adjustment of movements.

(2) *Spasticity and increase of reflexes.*—When well developed, the spasticity of a premotor lesion closely resembles that occurring in hemiplegia. The associated increase of reflexes is seen most prominently in the deep reflexes of the digits, i.e. the signs of Rossolimo, Mendel-Bechterew and Hoffmann, and those signs may persist after unilateral lesions in animals, even when spasticity has become slight or scarcely demonstrable [15, 20]. When bilateral lesions of the premotor area have been made, the degree of the spasticity, and possibly also of the increase of reflexes, varies with the animal's position in space, the extensors being most spastic when the animal lies on the affected side.

Of the superficial reflexes only the plantars have been studied experimentally; the phenomenon of lateral deviation of the toes appears to be a premotor symptom [15], sometimes associated with exaggerated plantar flexion. The case just reported showed exaggerated plantar flexion after operation, but there was little fanning of the toes.

(3) *Forced grasping* [8A].—The reflex grasping exhibited by the above

case was typical of that previously described in other cases by Adie and Critchley [1], Freeman and Crosby [8], Davis and Currier [5], and others [11, 25], in that it was brought on by stimulation of the palm of the hand at the base of the fingers, or by putting the flexor tendons of the fingers very slightly on stretch (Walshe and Robertson [25]). Voluntary relaxation, moreover, was difficult. This particular case showed the striking phenomenon first observed in experimental animals [2], namely, a variation in the strength of the reflex with change of the patient's body in space. That is, the reflex was exaggerated when the patient lay on his right side with the affected extremity uppermost, and was diminished with the patient on his left side. This phenomenon has been observed experimentally after extirpation of the premotor area in monkeys [2], and was also seen by Magnus in 1922 [17] in thalamic monkeys. The increased force of flexion of the digits in the uppermost extremities is a part of the pattern of righting reflexes in thalamic preparations as it is in the monkeys with bilateral cortical extirpations of the premotor and motor areas. The same phenomenon, but less marked, appears for a short time after unilateral extirpation of the premotor area in monkeys, and it is of this type that the response must be in the present patient in whom the lesion is unilateral.

(4) *Vasomotor changes.*—The changes in the temperature of the skin on the left side in this patient are likewise of interest, as they would seem to indicate a cortical control of sweating and of the vasomotor system. It is a well-known clinical fact that patients with hemiparesis frequently show œdema and vasodilatation of the affected extremities, but this has usually been attributed to disuse. In this patient the temperature changes were present, without paresis, and affected face, ear and leg, as well as the left upper extremity. Gowers [10, vol. ii, p. 77], in 1888, was fully aware of the relation between the cortex and skin temperatures. Thus he describes vasomotor and "trophic" changes associated with cortical and capsular lesions in the following terms:—

"*Vasomotor and trophic changes.*—The paralysed limbs: (1) May present no vascular changes; (2) they may be warmer by half a degree or so than those of the opposite side; (3) they may be colder, pale or livid. Eulenberg and Landois have ascertained that the cortex contains, near the motor centres for the limbs, other centres that influence the vascular state of the limbs. Irritation of these centres causes pallor and coldness, while hyperæmia and increased warmth are probably the result of a loss of the central influence and may be due to disease of the cortex or of the path from it, which seems to pass in the posterior limb of the internal capsule. The elevation of temperature may be from 0·2° to 1·5° F. above that of the unparalysed side. It is often uniformly raised for ten

days or a fortnight, and then presents variations, sometimes an elevation, sometimes a depression. The elevation of temperature may be accompanied by redness of the skin; when the temperature falls the vessels may remain distended, and the limb then has a bluish-red aspect. Occasionally there is increased sweating. There may be some œdema of the subcutaneous tissue, most marked towards the extremity of the limb. This, in slight degree, is very common, and may come on at the end of one or two days and persist for many weeks."[1]

In the subhuman primates there is always a change in skin temperature of the contralateral extremities following lesions of the premotor areas [14], but whether this is due to a change in the mechanism of sweating or to primary disturbance of vasomotor control has not yet been determined experimentally. Further analysis is also needed of the anatomical position of the vasomotor area.

IV.—Conclusions.

(1) A case of forced grasping is presented which, like other cases described in the clinical literature, exhibited spasticity, increase of the tendon reflexes of the digits, and gradual impairment of skilled movements of the fingers. These symptoms, together with vasomotor disturbances of the affected extremity, form a well-defined clinical entity which we have designated "the syndrome of the premotor cortex." All manifestations of the condition can be reproduced experimentally in the subhuman primates by lesions restricted to the premotor area.

(2) The premotor syndrome may be distinguished clinically from the motor-area syndrome on the basis of the chronology of symptoms. With premotor lesions, awkwardness, spasticity and increase of tendon reflexes appear early before the onset of motor weakness; whereas in lesions of the motor area weakness begins early, reflexes are at first depressed, and spasticity, if present, appears late.

(3) The forced grasping in the case herein described showed consistent variations with changes of position of the body in space, which places the phenomenon in the category of the righting reflexes described by Magnus [2, 8A].

(4) The changes in skin temperature and sweating on the side opposite the lesion indicates that representation of the autonomic nervous system exists in the cortex.

[1] The work of Eulenberg and Landois [6] demonstrated that stimulation of the region of the cruciate sulcus of dogs caused a change of temperature in contralateral extremities, whereas stimulation of the other areas of the cortex cause no such alteration.

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Notices of Recent Publications.

Anatomie du Système Nerveux. Par C. Winkler. Haarlem: Erven F. Bohn. 1933. Pp. 367. 5me Partie.

It is fifteen years since the first volume of Professor Winkler's "Anatomy of the Nervous System" appeared, and those interested in this fundamental aspect of neurology have welcomed the succeeding parts which have been published in the interval. The present volume, which is devoted to the corpus striatum and the diencephalon, completes the system, for the author has unfortunately decided that the time is not yet ripe to describe fully the anatomy of the cerebral cortex and discuss its functional relationships.

The work has been a noteworthy achievement; it has undoubtedly a permanent value and will occupy an important and useful place among the many textbooks devoted to the anatomy of the nervous system. It bears the stamp of its author's individuality and is obviously based mainly on his own study and researches; in no sense is it a compilation. As the author is primarily a clinician it is natural that attention is directed mainly to those subjects that may have a practical application, in fact in its subtitle the volume is represented as an attempt to present as separate functional systems the tracts and centres by which sensory impressions are translated into reflex reactions.

In the first half of the book the anatomy and connections of the corpus striatum, which daily claim more attention owing to the increasing recognition of the rôle this part plays in the regulation of movement, are fully described. The author is uncertain whether the pallidum is devised from the telencephalon or diencephalon. On embryological grounds he recognizes a distinction between its occipital and frontal parts and believes that there is a functional distinction too, the latter being concerned in the dynamic mechanisms which effect co-ordinated movements, the former in the postural reactions of the trunk and limb girdles (the myostasis of Kleist). He accepts the existence of striopetal fibres from the cerebral cortex.

Owing to the complexity of the diencephalon, its separate parts, the epithalamus, the thalamus proper and the hypothalamus, are first described systematically in the simple brain of the rabbit and later in the human brain. From the physiological point of view the thalamus is regarded as an organ concerned in the simpler integration of sensations.

The printing of the volume and the reproduction of the numerous illustrations which it contains deserve the high praise of being worthy of the subject.

Weitere Beiträge zur Pathologie der traumatischen Gehirnblutungen. Von O. BERNER. Oslo: Jacob Dybwad. 1933. S. 105.

Many years ago Duret drew attention to the frequency of small hæmorrhages around the aqueduct of Sylvius and in the floor of the fourth ventricle in the brains of persons dying from cerebral trauma, and attributed to these lesions an important rôle in the production of the symptoms of cerebral concussion. He regarded these small hæmorrhages as the result of an abrupt wave of cerebrospinal fluid impinging on the grey matter of the aqueduct and ventricle. Duret's observation and views received at the time of their publication considerable support from both pathologists and experimenters, but within recent years they have been largely neglected; in some recent monographs on cerebral trauma they are not even referred to.

Berner, of Oslo, has examined the brains of a large series of suitable cases and he has in almost all discovered the lesions described by Duret. In many cases these hæmorrhages are visible to the naked eye, but in others they can be demonstrated only in microscopical sections. In the fourth ventricle they lie chiefly near the middle line in front of the striæ acusticæ and in the anterior part of the mid-brain below the aqueduct. Larger hæmorrhages may be found in the grey matter of the pons. They are probably due to diapedesis rather than to rupture of vessels, and may be explained by Duret's hypothesis. Berner concludes that many of the symptoms of cerebral concussion are due to these circulatory disturbances in the medulla and pons.

This monograph is evidently based on a careful and methodical investigation, and cannot be neglected by anyone interested in the symptoms and pathogenesis of cerebral concussion.

La Syphilis du Cervelet et des Connexions cérébelleuses. Par J. THEIRS. Paris: G. Doin et Cie. 1934. Pp. 194. Price 20 fr.

Syphilis affects the cerebellum in much the same manner as it does other parts of the central nervous system, but as the lesions are generally due to occlusions of, or hæmorrhages from, vessels which supply the brain-stem too, the resulting symptoms are rarely referable to the cerebellum alone. Thiers has collected from recent French literature a number of observations, the causal lesions of which were of syphilitic origin, and attempts to group them into syndromes, many of which it must be said are artificial or unnecessary. The greater part of this monograph deals with "syphilitic cerebellar hemiplegia." In a few cases the lesions are purely cerebellar, but frequently the symptoms are due to affections of the cerebellar connections and they are then often associated with disturbances of cerebral, mesencephalic or pontine origin. Fuller descriptions of the lesions producing these syndromes would have been welcome. Gummata of the cerebellum and cerebellar lesions occurring in the course of the syphilitic disease of the nervous system are also considered.

Pink Disease (Infantile Acrodynia). By CH. ROCAZ. Translated by I. J. WOOD, M.D. London: Martin Hopkinson, Ltd, 1933. Pp. 153. Price 7s. 6d.

This small monograph brings the subject up to 1931, the date of the French edition. It gives a very full account of the symptoms and of what is known of the pathology of the condition, which the author considers to be produced by a primary disturbance of the neuro-vegetative system. He is inclined to accept Kuiper's view that the primary lesion is in the diencephalic nuclei; indeed he regards it as a form of encephalitis affecting this region of the brain. In favour of this theory he cites the initial pyrexia and the early lymphocytosis in the cerebrospinal fluid. The disease resembles encephalitis lethargica in the nocturnal insomnia with drowsiness by day, the myoclonus and the changes in temperament.

The English translation in some places follows the French idiom rather too closely, but it is for the most part clear. There is a full bibliography, but no index.

Human Mentality. An Outline of General Psychiatry. By BROR GADELIUS. Copenhagen: Levin and Muskgaard. London: Humphrey Milford. 1933. Pp. 620. Price 30s.

Dr. Gadelius had until recently been for many years the Professor of Psychiatry in Stockholm, and this work was originally written to supply the lack of a Swedish textbook on the subject. The present volume is only half of the complete work; the remaining section deals with special psychiatry and no English translation of it has yet been published. It would be very welcome.

This book, written in clear and agreeable English, is informed by a psychological and psychotherapeutic interest. The author emphasizes how closely akin are the normal and the morbid phenomena in this field, and one has as a result a valuable presentation of psychopathology, erring neither on the academic nor the analytical side. Such an empirical psychology, as conceived by an experienced psychiatrist, is nearer to the facts with which the physician must deal than are the schemes of laboratory psychologists or of Freudians. To the latter Dr. Gadelius devotes a temperate but critical chapter, in large measure adverse.

The bulkiness of the volume is due to the author's intentional avoidance of a concise mode of presentation, for reasons which seem hardly valid in a textbook. It is, however, very easy to read, learned but not abstruse, and interesting; wide acquaintance with recent research is associated with sound judgment and excellent case-material. It would be impossible to name any other work which so happily demonstrates to the average reader that a true psychiatric psychopathology is being built up which is close to its material and

as fruitful therapeutically as in other ways, though restrained in its hypotheses and its application.

There are three sections, preceded by a historical and an epistemological survey. The first section deals with normal and morbid psychology or "functional structure of mental life," the second with the genetic and other causes of mental disease, and the third with treatment. The mode of approach throughout the book is individual but sound.

Sémiologie du Sommeil. Par A. TOURNAY. Pp. 131. Paris: G. Doin et Cie. 1934. Price 30 fr.

The interest in the nature of sleep which has been excited by recent physiological and pathological observations has led to the appearance of many monographs, but few of them are more comprehensive than, and yet so concise as, this book by Dr. Tournay. In the first two sections he describes carefully and analyses the bodily phenomena associated with sleep, as the state of the motor system, sensation, the special senses and the reflexes, as well as the visceral and metabolic activities. The second half of the book is concerned with the reciprocal influence of the cortex and subcortical parts of the nervous system in determining sleep and waking, and in a discussion of the probable nature of their activities in relation to sleep. The author brings no new facts to this discussion, but his clear and impartial summary of pathological and experimental observations will be of service to those unable to study the original publications and to all interested in this important biological problem.

Recent Advances in Psychiatry. By HENRY DEVINE. Second Edition. London: Churchill. 1933. Price 12s. 6d.

The second edition of this compendium of recent work has been enlarged to include chapters on heredity in mental disorder and on deficient oxidation, as well as a short one describing the mental concomitants of pernicious anæmia. The book bears everywhere the impress of Dr. Devine's wide acquaintance with the literature of the subject and of his tolerant and receptive attitude towards tendencies and schools commonly thought to be violently opposed or even fundamentally irreconcilable. This has led to the retention of some material now generally thought to be unsound, but the impartiality of the presentation is very evident. There can be no doubt of the value of such a work for English readers.

Nouveau Traité de Psychologie. Par GEORGES DUMAS. Tome troisième. Les Associations sensitivo-motrices. Pp. 462. Paris: Alcan. 1933. Price 100 fr.

The third volume of this very useful system of psychology is like its predecessors in its succinct, though detailed, mode of critical presentation and in its attention to work done in other countries besides France, though often

the most recent foreign work is overlooked. The present volume is the work of two contributors, Professor Georges Dumas and André Ombrédane. It deals with the higher sensori-motor integration. Ombrédane gives a clear and penetrating review of the experimental data and conclusions regarding equilibrium and orientation. The following two sections, by Dumas, occupy the greater part of the book. The first is concerned with the expression of emotion and the second with expressive mimicry. Professor Dumas has been active in this field since the beginning of the century, and his recent studies on congenitally blind persons are of particular interest. His survey of the subject here is a notable contribution to a difficult and unduly neglected branch of psychology. The concluding section of the volume, on language, is by Ombrédane. It is brief, but this is a rare and welcome feature in writing on this subject. The writer is closely attached to the teachings by Charles Foix which aim at a cerebral localization of speech in two planes, as it were. He presents summarily the conflicting views on the pathological aspects of language but scarcely does justice to the work of the German school, represented by Goldstein, nor is there in this section a satisfying discussion of the problem of inner speech and its relation to thinking. On the whole this volume admirably fulfils its purpose.

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EDITOR.